CONTENTS

The American Journal of Medicine

Vol. XVI FEBRUARY, 1954 No. 2

Editorial

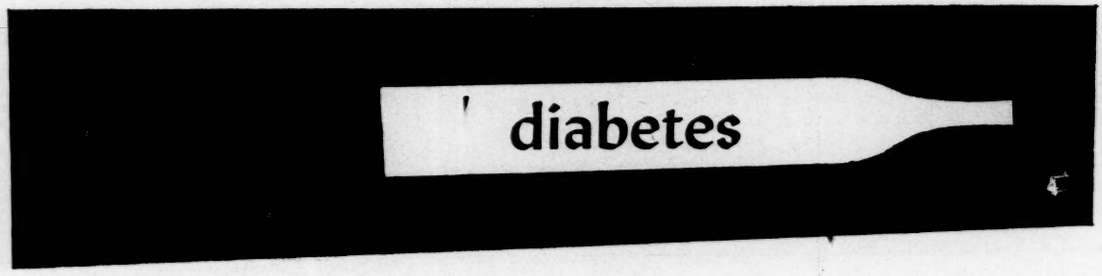
Clinical Studies

As part of a general survey by the American Council on Rheumatic Fever, a study was made of the comparative therapeutic efficacy of aspirin, ACTH and cortisone on the manifestations of acute rheumatic fever in 148 young adult males. While no conclusions as to effects on the incidence of persistent valvular or myocardial lesions can be drawn, because of the short period of observation, the results clearly indicate that there is little to choose among these three agents in regard to control of acute symptoms and signs of rheumatic fever.

In one of the most adequate studies on phenylbutazone which has yet appeared, the authors summarize present knowledge concerning the physiologic disposition of the drug and report in detail their observations on its effects in eighteen patients with rheumatoid arthritis. The clinical response was about the same as obtained with cortisone or corticotropin, as indicated by direct comparison in most instances. There is also a similar effect in respect to salt and water retention but that the action of phenylbutazone is not mediated through the adrenal cortex is clearly indicated by various significant differences. In an over-all series of eighty-seven patients treated with phenylbutazone for protracted periods by these investigators, undesirable drug effects necessitated discontinuance of therapy in 20 per cent of cases, in no instance in their experience, however, owing to bone marrow depression.

The sensitized sheep cell agglutination test is an important recent addition to methods for laboratory confirmation of the diagnosis of rheumatoid arthritis. The results of this careful study conform to the general experience that this test is highly specific for rheumatoid arthritis but is un-

Contents continued on page 5



"the ideal detection center is the office of the family physician"[1]

Found: 20,255 "new" diabetics in one year in the private practice of 5000 physicians responding to a nationwide poll. Of these, 81% were detected by urine-sugar analysis; 62% of the physicians used *Clinitest*.

"Only 19% of the diabetics in this survey were detected by findings other than glycosuria. Every patient therefore, should have at least one urinalysis as part of his examination, even if the purpose of his visit is only the removal of wax from the ears."[2]

CLINITEST®

BRAND

for detection of urine-sugar

*Data from nationwide poll: Diabetes in daily practice

70% were over 40
40% had a family history of diabetes
65% were overweight

1. Blotner, H., and Marble, A.: New England J. Med. *245*:567 (Oct. 11) 1951.
2. Steine, L.: GP *8*:45 (July) 1953.

Ames Diagnostics
Adjuncts in clinical management

AMES
COMPANY, INC. • ELKHART, INDIANA
Ames Company of Canada, Ltd., Toronto

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CONTENTS

The American Journal of Medicine

Vol. XVI FEBRUARY, 1954 No. 2

Contents continued from page 3

Contents continued on page 7

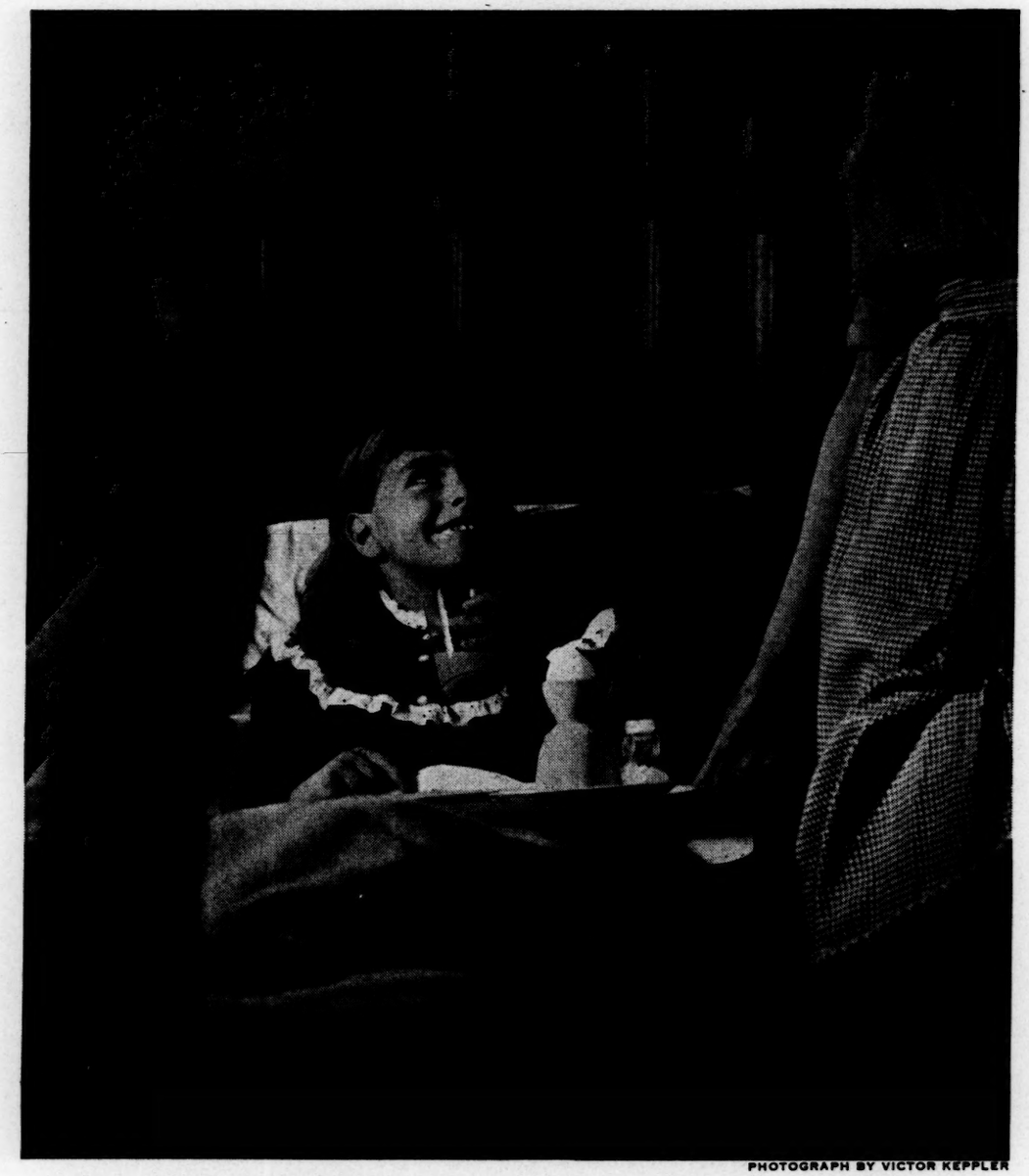
CONTENTS

The American Journal of Medicine

Vol. XVI FEBRUARY, 1954 No. 2

Contents continued from page 5

Contents continued on page 9



PHOTOGRAPH BY VICTOR KEPPLER

"Now I can swallow easily—my throat's much better"

TRACINETS®

BACITRACIN-TYROTHRICIN TROCHES WITH BENZOCAINE

Your patients will like TRACINETS because they really soothe irritated throats—taste good, besides.

Two topical antibiotics combined, bacitracin and tyrothricin, give your patients double antibacterial action, while benzocaine provides a soothing, anesthetic effect. In severe throat infections, TRACINETS conveniently supplement systemic therapy.

Quick Information: Each troche contains 50 units of bacitracin, 1 mg. of tyrothricin, 5 mg. of benzocaine. In vials of 12.

CONTENTS

The American Journal of Medicine

Vol. XVI FEBRUARY, 1954 No. 2

Contents continued from page 7

hepatic circulation indicating the extraordinary complexity of blood channels through the liver and the intricacies of regulation of hepatic blood flow. It was possible to do little more than catalogue the many and varied other aspects of liver physiology, including comments on the bile and the gallbladder.

Clinico-pathologic Conference

Case Reports

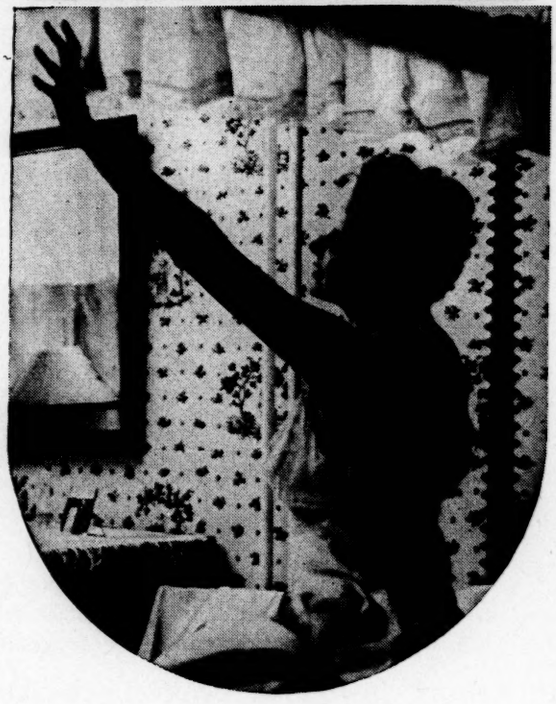
Advertising Index on 3rd Cover

Change of address must reach us one month preceding month of issue.

SLEEPYHEAD TONIGHT...

CLEAR HEAD TOMORROW

ETHOBRAL—the NEW, *triple* barbiturate—promotes nightlong sleep . . . with fast, clear-headed awakening. More than 90 per cent of patients in one study[1] had no morning after-effects . . . no lassitude . . . no depression. Sleep is induced . . . sustained . . . then the effects dissipate rapidly.



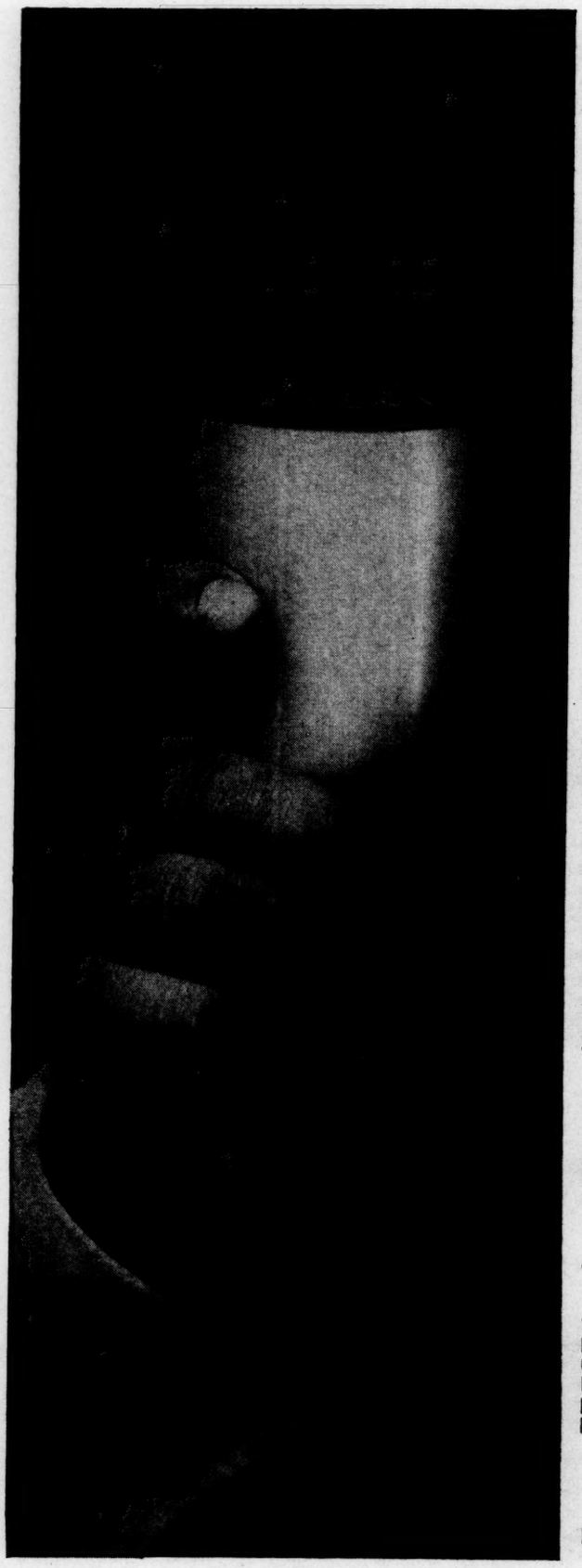
ETHOBRAL combines secobarbital, butabarbital, phenobarbital in *judicious balance.* Contains just enough of each component to foster effective sleep . . . without burdening the patient on awakening. One capsule is usually adequate.

1. DeShong, H. C.: to be published

Each ETHOBRAL capsule contains:
Sodium Secobarbital 50 mg. (¾ gr.)
Sodium Butabarbital 30 mg. (½ gr.)
Phenobarbital 50 mg. (¾ gr.)
Supplied: Bottles of 100 and 500 capsules

NEW!
ETHOBRAL®
Triple - Barbiturate Capsules

Wyeth®
Philadelphia 2, Pa.



"To Your Patient's Health!"

Good nutrition and good health go hand in hand! Knox Concentrated Gelatine Drink is a worthy protein dietary adjuvant where high protein diet is indicated.

First used by the profession in this form about fifteen years ago, increasing clinical usage demonstrates its professional acceptance. Up to 60 grams of Knox Gelatine in the concentrated drink have been administered daily with no allergic reactions.[1] It contains 25 per cent glycine and 7 out of 8 essential amino acids, as well as 9 other accepted aminos. Knox Gelatine is low in sodium, has a pH of 6.2-6.4, is pure protein with no sugar and no flavoring.

1. Reich, C., and Mulinos, M. G., Treatment of Refractory Nutritional Anemia with Gelatine. Bull. N. Y. Med. Coll. March 1953.

How to Administer Knox Gelatine Concentrate Drink!

Each envelope of Knox Gelatine contains 7 grams which the patient is directed to pour into a ¾ glass of orange juice, other fruit juices, or water, not iced. Let the liquid absorb the gelatine, stir briskly, and drink at once. If it thickens, add more liquid and stir again. Two envelopes or more a day are average minimal doses. Each envelope contains but 28 calories.

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Be sure you specify KNOX so that your patient does not mistakenly get factory-flavored gelatine dessert powders which are 85% sugar.

You are invited to send for brochures on diets of Diabetes, Colitis, Peptic Ulcer... Low Salt, Reducing, Liquid, and Soft Diets. KNOX GELATINE, JOHNSTOWN, N.Y. Dept. AJM-2

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the realization of a hope . . .

. . . for a satisfactory preparation in the management of hypercholesteremia

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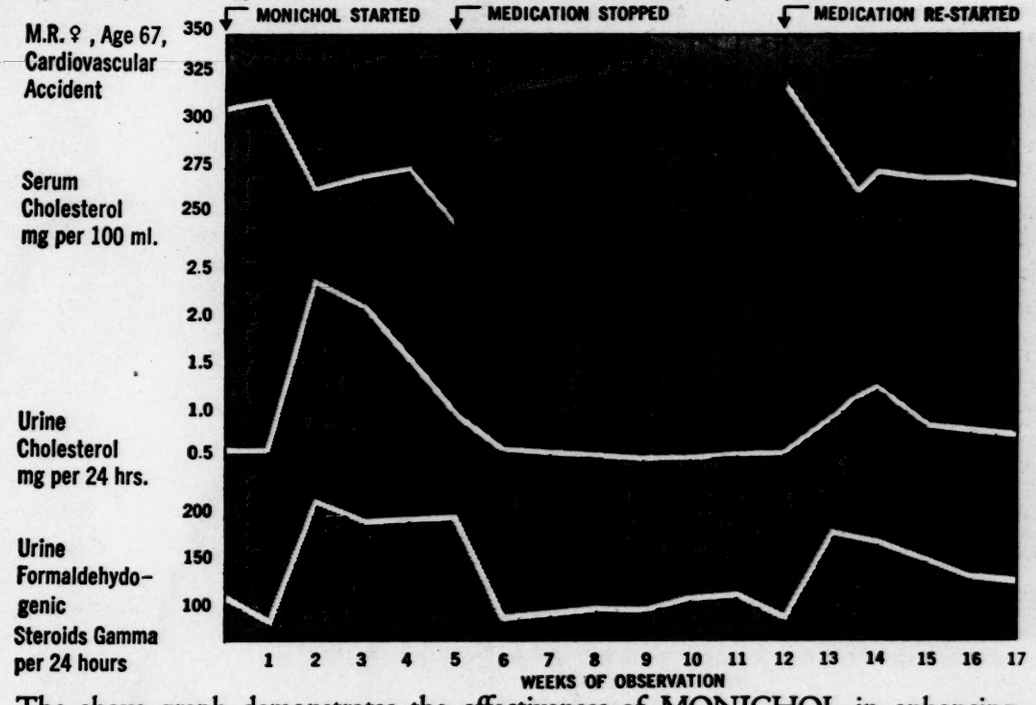
I.V.C.®

Typical Response of a Hypercholesteremic Patient to 20 cc. of MONICHOL* Daily in Divided Doses**



The above graph demonstrates the effectiveness of MONICHOL in enhancing the stability of the serum lipid emulsion by: ▲ normalizing elevated serum cholesterol levels, ● changing the character of the excess serum cholesterol to facilitate urinary excretion, and ■ making the excess serum cholesterol more readily available for utilization by the adrenal cortex in steroid synthesis.**

The sense of well-being experienced by patients on MONICHOL is attributed by the investigators** to better utilization of excess serum cholesterol by the adrenal cortex. MONICHOL is entirely non-toxic.

The red portion of the graph shows that uninterrupted daily intake of MONICHOL is essential, because hypercholesteremia is probably due to an inborn error of metabolism.

Indications: For the therapeutic and prophylactic management of hypercholesteremia so frequently associated with cardiovascular disease and diabetes.

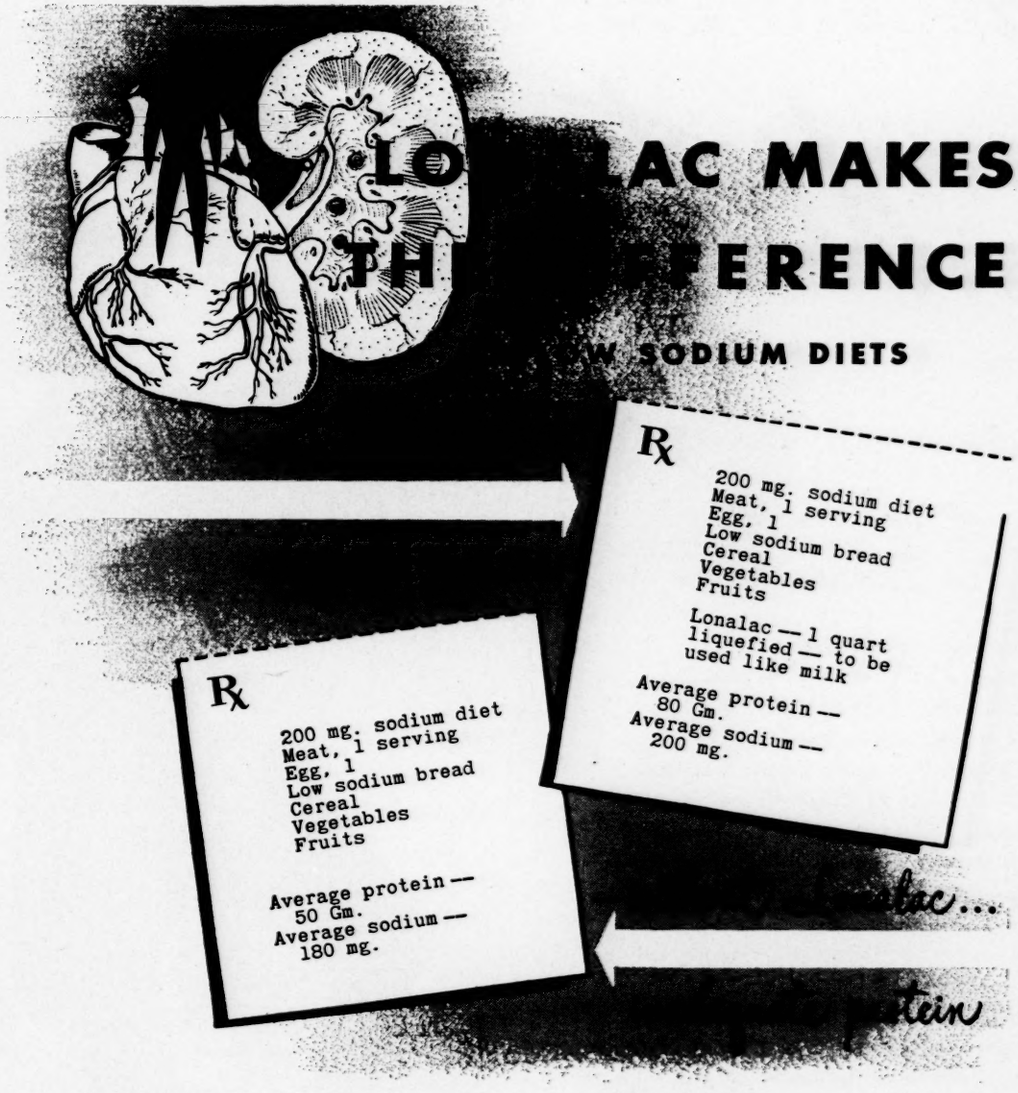
Formula: Each teaspoonful (5 cc.) contains:		Minimum Dosage: Two teaspoonsful twice daily after meals.
Polysorbate 80	500 mg.	Supplied: Bottles of 12 oz.
Choline Dihydrogen Citrate	500 mg.	
Inositol	250 mg.	Literature on request

**Sherber, D. A., and Levites, M. M.: Hypercholesteremia. Effect on Cholesterol Metabolism of a Polysorbate 80-Choline-Inositol Complex (MONICHOL) J.A.M.A. 152:682 (June 20) 1953.

*Trademark

Monichol normalizes cholesterol metabolism

IVES-CAMERON COMPANY, INC., 22 East 40th Street, New York 16, N. Y.



Nutritionally similar to whole milk but with negligible sodium content, Lonalac solves the problem created by the high sodium content of the usual protein foods.

When sodium intake must be sharply restricted, protein deficiency is seriously threatened . . . since meat and eggs can be used only in small quantities and milk, with its still higher sodium content, usually must be eliminated.

With Lonalac supplying the protein equivalent of milk, the patient's nutritional needs can be generously met, even on a 200 mg. sodium diet.

Lonalac is used just as milk is used, as a beverage and in soups, muffins, desserts, etc. It permits varied and appetizing meals that encourage patients to adhere to a low sodium regimen.

Lonalac is virtually free of cholesterol.

Lonalac is supplied in 1 pound and economical 4 pound cans. Low sodium diet outlines suitable for use by patients are available on request.

Lonalac

The low sodium, high protein food

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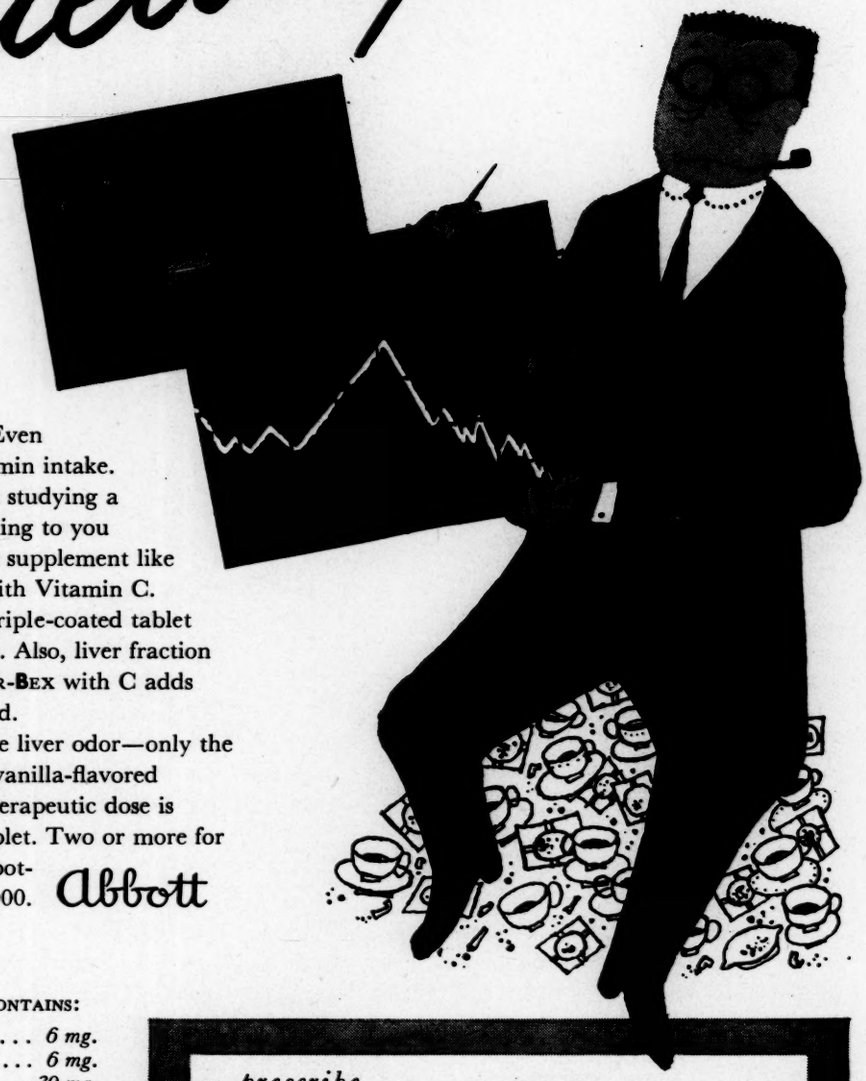
Eminent Economist ...dietary dub



HE KNOWS ECONOMY. Even economizes on his vitamin intake.

Eventually, he'll be studying a corrected diet and looking to you for a potent B-complex supplement like SUR-BEX or SUR-BEX with Vitamin C.

Each compressed, triple-coated tablet provides six B vitamins. Also, liver fraction and brewer's yeast. SUR-BEX with C adds 150 mg. of ascorbic acid.

No trace of offensive liver odor—only the pleasant aroma of the vanilla-flavored sugar coating. Daily therapeutic dose is one easy-to-swallow tablet. Two or more for severe deficiencies. In bottles of 100, 500 and 1000. Abbott

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Thiamine mononitrate	*6 mg.*
Riboflavin	*6 mg.*
Nicotinamide	*30 mg.*
Pyridoxine hydrochloride	*1 mg.*
Vitamin B_{12} (as vitamin B_{12} concentrate)	*2 mcg.*
Pantothenic acid (as calcium pantothenate)	*10 mg.*
Liver fraction 2, N.F.	*0.3 Gm. (5 grs.)*
Brewer's yeast, dried	*0.15 Gm. (2½ grs.)*

SUR-BEX WITH VITAMIN C contains 150 mg. of ascorbic acid in addition to the vitamin B complex factors.

prescribe

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(ABBOTT'S VITAMIN B COMPLEX TABLETS)

or **SUR-BEX** *with* **C**

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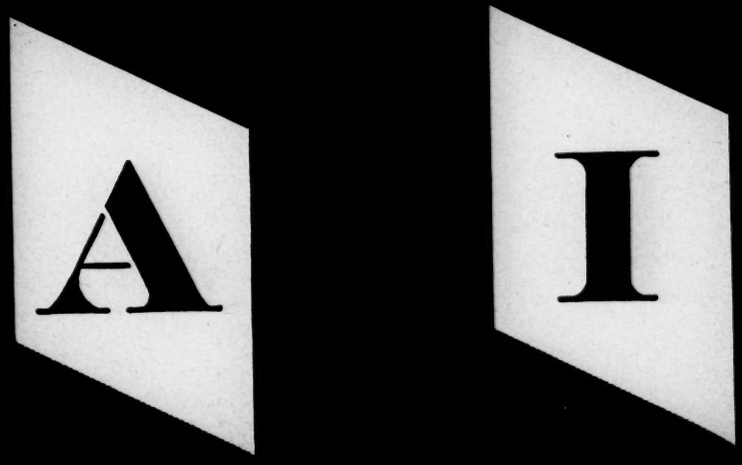
A new, potent antibacterial—

Gantricillin-300 'Roche'

...for wide-spectrum antibacterial therapy: GANTRICILLIN®-300 'Roche.' Each tablet provides 300,000 units of penicillin PLUS 0.5 Gm of Gantrisin®, the single, highly soluble sulfonamide.

Combined antibacterial therapy —

...with the new Gantricillin®-300 tablet 'Roche.' A convenient way of administering 300,000 units of penicillin PLUS 0.5 Gm of Gantrisin®, the single, soluble sulfonamide.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J. B. Roerig and Company announces the availability of

agent

pneumococcal infections, including pneumonia, with or without bacteremia.

streptococcal infections, with or without bacteremia, including follicular tonsillitis, septic sore throat, scarlet fever, pharyngitis, cellulitis, urinary tract infections due to susceptible organisms, and meningitis.

many staphylococcal infections, with or without bacteremia, including furunculosis, septicemia,

abscesses,
impetigo,
acute otitis media,
ophthalmic infections,
susceptible urinary tract infections,
bronchopulmonary infections,
acute bronchitis,
pleurisy,
[illegible],
[illegible],
cellulitis,
tonsillitis,
otitis media,
osteomyelitis,
[illegible],
[illegible],
[illegible].

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among broad-spectrum antibiotics

BASIC chemically... its structure is the nucleus of modern broad-spectrum antibiotic activity

racyn

Brand of tetracycline hydrochloride

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it has a wide range of antimicrobial action in vitro and in vivo

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TETRACYN INTRAVENOUS Vials of 250 mg., and 500 mg.
TETRACYN ORAL SUSPENSION *(amphoteric) (chocolate-flavored)*
Bottles of 1.5 Gm.; provides 250 mg. per 5 cc. teaspoonful

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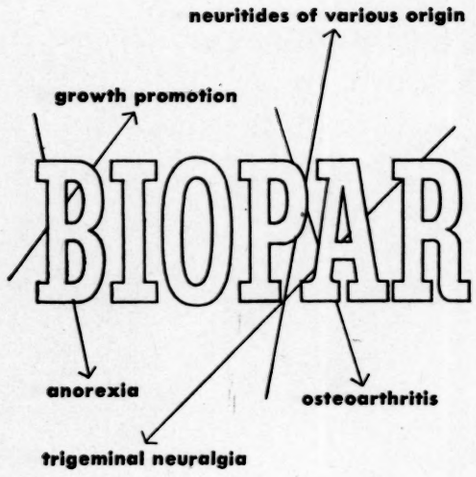

BIOPAR is "intrinsically" better

A new, many times more potent Intrinsic Factor in Biopar makes possible a full therapeutic vitamin B_{12} response orally—even in the presence of partial or complete achlorhydria. The Intrinsic Factor in Biopar, many times more active than previously available intrinsic factor preparations—performs the essential functions ascribed to the classic Intrinsic Factor of Castle.

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Oral Biopar therapy produces a full reticulocyte response and red blood cell increment in pernicious anemia, as confirmed by fourteen independent investigators (personal communications).

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Each BIOPAR tablet contains:
Crystalline Vitamin B_{12} U.S.P.... 6 mcg.
Intrinsic Factor... .....30 mg.
Supplied: Bottles of 30 tablets.

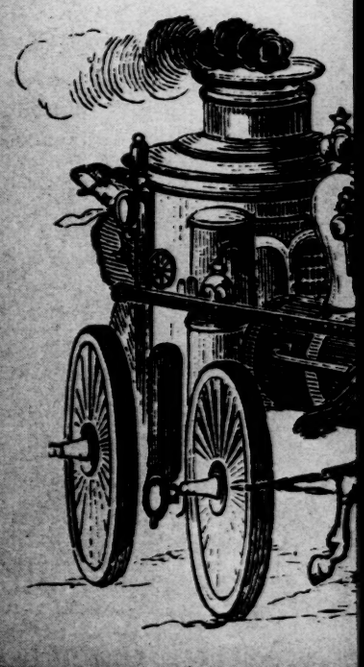
THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY · CHICAGO 11, ILLINOIS

new

pt

in anti-inflammatory therapy

new



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Cortril tablets

brand of hydrocortisone

Studies indicate that hydrocortisone is the predominant natural anti-inflammatory hormone, and extensive investigations have demonstrated its superior therapeutic efficacy.

Clinical reports comparing hydrocortisone with cortisone note that hydrocortisone produces maximal therapeutic benefits with smaller initial and maintenance dosage requirements and decreased endocrine complications.[1,2]

Cortril
of proved therapeutic merit in:

Rheumatoid arthritis
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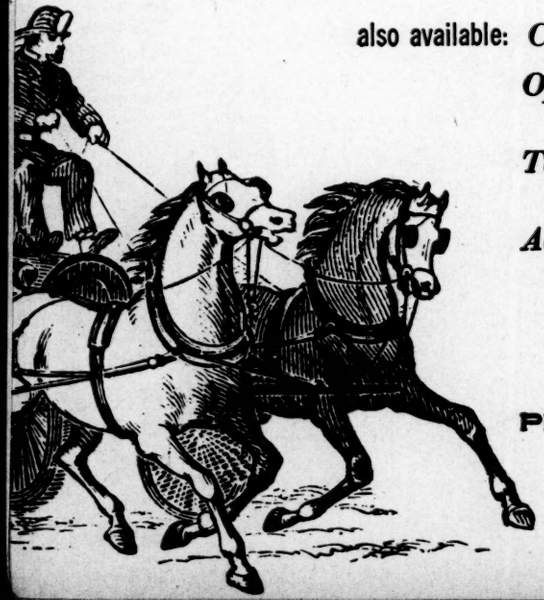
Acute rheumatic fever
Addison's disease
Bronchial asthma
Acute and chronic ocular disorders and other conditions responsive to systemic adrenocortical hormone therapy

supplied: **CORTRIL Tablets,** *scored, 20 mg., in bottles of 20.*



also available: ***CORTRIL Acetate***

Ophthalmic Ointment
in 1/8-oz. tubes in strengths of 0.5% and 2.5%

Topical Ointment
in 1/6-oz. tubes in strengths of 1.0% and 2.5%

Aqueous Suspension for intra-articular injection
in 5-cc. vials, 25 mg. per cc.

PFIZER SYNTEX PRODUCTS

new

Anti-inflammatory and anti-infective management in ocular disorders

Cortril acetate ophthalmic suspension

brand of hydrocortisone acetate

with Terramycin® hydrochloride

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New therapeutic approach in ocular disorders

The combination in one preparation of CORTRIL, the topically effective anti-inflammatory hormone, and TERRAMYCIN, the broad-spectrum antimicrobial agent, represents a new attainment in ophthalmologic therapy.

Clinical studies reveal that topical hydrocortisone is significantly superior to cortisone[3,4,5] in reducing local edema and controlling excessive tissue reactions due to allergens, infection, or trauma in diseases of the anterior segment of the eye.

TERRAMYCIN, with its broad antimicrobial spectrum, is an antibiotic of choice to curtail the growth of primary or secondary infecting organisms. Thus in ocular inflammation where infection coexists, is suspected, or anticipated, administration of CORTRIL Ophthalmic Suspension with TERRAMYCIN provides unexcelled therapy.

Cortril with Terramycin *of distinct advantage in:*

- **Blepharitis**
- **Conjunctivitis**
- **Corneal ulcer and other corneal afflictions**
- **Scleritis**
- **Iritis and other conditions responsive to topical adrenocortical hormone therapy**

supplied: Each cc. of CORTRIL Acetate Ophthalmic Suspension with TERRAMYCIN, sterile, contains 15 mg. of CORTRIL acetate and 5 mg. of TERRAMYCIN hydrochloride, in amber bottles of 5 cc. with a sterile eye dropper.

references:
1. Boland, E. W.: Ann. Rheum. Dis. 12:125, 1953. 2. Boland, E. W.: California Med. 77:1, 1952. 3. Laval, J.: A.M.A. Arch. Ophth. 59:299, 1953. 4. McDonald, F. R.; Leopold, I. H.; Vogel, A. W., and Mulberger, R. D.: A.M.A. Arch. Ophth. 49:400, 1953. 5. Steffensen, E. H.: J.A.M.A. 159:1660, 1952.

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Division, Chas. Pfizer & Co., Inc.
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Rauvera

- **RAUWOLFIA SERPENTINA ALKALOIDS**
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THE ADVANTAGES OF COMBINING RAUWOLFIA SERPENTINA and VERATRUM VIRIDE

Many cardiologists today assert that in hypertension, combination therapy is more effective than any one drug alone. The combination of Rauwolfia serpentina and Veratrum viride, as provided by Rauvera, is considered one of the more desirable mixtures. Only mildly hypotensive in its action, Rauwolfia serpentina leads to striking subjective improvement, lowers dosage requirements of Veratrum viride, and reduces the incidence of reactions to the latter. The combination exerts a remarkable additive, if not synergistic, influence.

● THE DISTINCTIVE ACTION OF RAUWOLFIA SERPENTINA

Exerting a mild hypotensive influence, Rauwolfia serpentina also produces: relaxing sedation, bradycardia —not tachycardia, and relief of headache and dizziness. By inducing a state of calm tranquility, it creates a sense of well-being and a more favorable outlook. Rauvera contains a highly purified extract of Rauwolfia serpentina alkaloids, the alseroxylon fraction, which is tested in dogs for its hypotensive, sedative, and bradycrotic actions.

● THE POTENT HYPOTENSIVE ACTION OF VERATRUM VIRIDE

Termed one of the safest of the more potent hypotensives, Veratrum viride lowers blood pressure by central action. Like Rauwolfia serpentina, it does not interfere with the postural reflexes, since it is not ganglionic or adrenergic blocking. Its influence is exerted promptly, in contrast to that of Rauwolfia serpentina, which may take weeks to develop to maximum intensity.

IN MODERATE AND SEVERE ESSENTIAL HYPERTENSION

Because of its potent hypotensive activity, Rauvera is indicated in moderate, severe, and resistant essential hypertension. Subjective relief is prompt, the patient is not incapacitated because the postural reflexes remain intact, and the blood pressure is lowered significantly. Each scored Rauvera tablet contains 1 mg. of Rauwolfia serpentina alkaloids and 3 mg. of Veratrum viride alkaloids (alkavervir). Average dose, 1 tablet 3 times daily, at intervals of not less than 4 hours, ideally after meals.

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a new broad-spectrum antibiotic

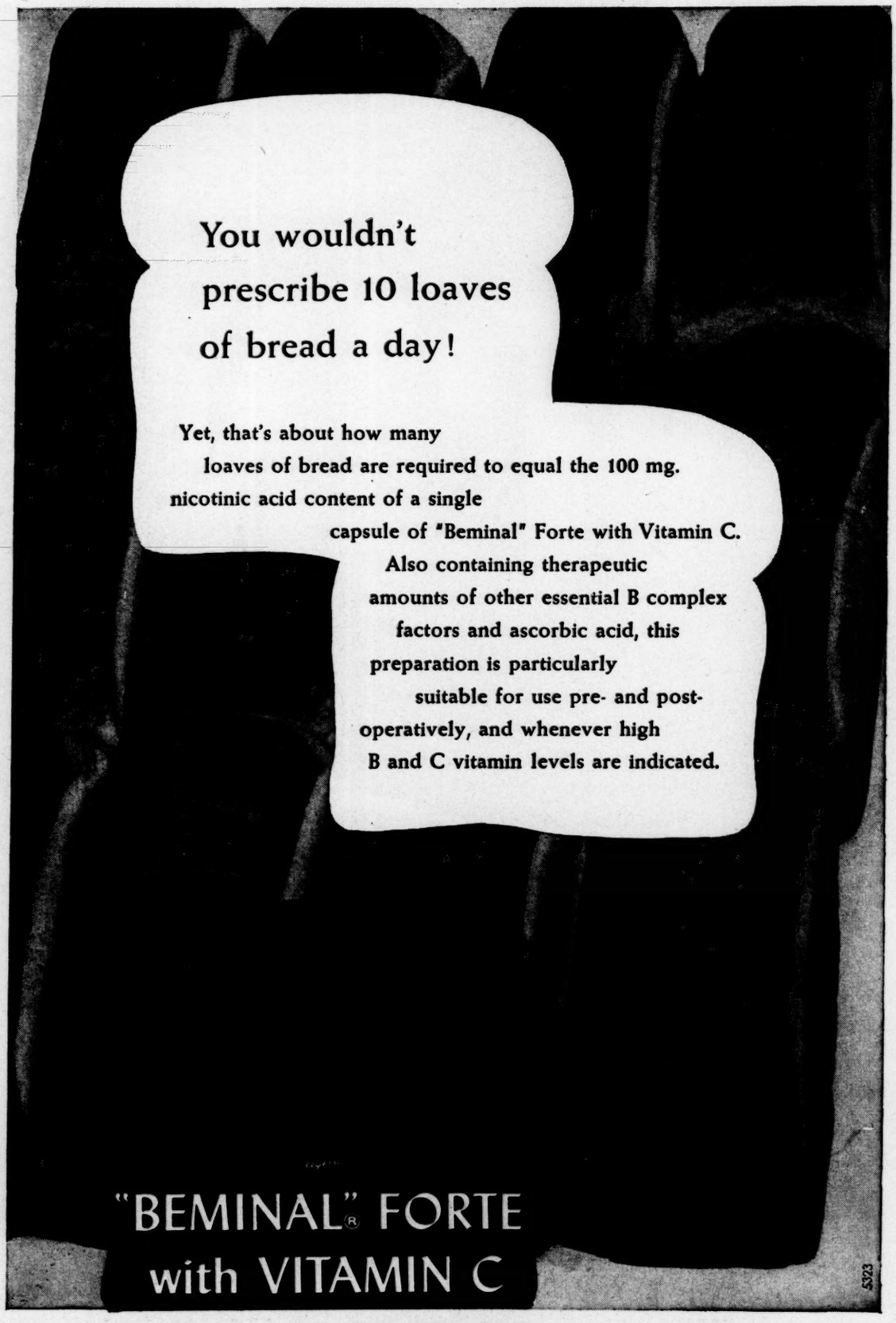
ACHRO

ACHROMYCIN is a new and superior broad-spectrum antibiotic, developed by Lederle research. ACHROMYCIN has demonstrated greater effectiveness in clinical trials with the advantages of more rapid absorption, quicker diffusion in tissue and body fluids, and increased stability resulting in prolonged high blood levels.

ACHROMYCIN has demonstrated effectiveness against pneumococcal and meningococcal infections; against Gram-negative cocci; against Gram-positive cocci; against Gram-negative bacilli; and against certain mixed infections.

CAPSULES { 250 mg. / 100 mg. / 50 mg. } **TABLETS** { 250 mg. } **INTRAVENOUS** { 500 mg. / 250 mg. / 100 mg. } **SPERSOIDS®** Dispersible Powder { 50 mg. per teaspoonful (3.0 Gm.) }

Other dosage forms will become available as rapidly as research permits.



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3 steps to better diagnosis

in Vascular Disturbances

#1 The Newest Development in Sphygmomanometers

THE MANUELL ANEROID combines a sturdy aneroid manometer with a new and long needed, practical design feature. The manometer is attached directly to the bulb held in the hand of the physician—where it belongs. Hooking or hanging the dial from the cuff on the patient's arm is no longer necessary. Minimum of patient anxiety and apprehension since only the physician can see the dial.

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List Price—with wrap-around cuff **$40.00**

Other Propper Sphygmomanometers include wall and desk model mercurials and regular aneroids of high quality at economy prices.

All models available with wrap-around or hook-on cuff.

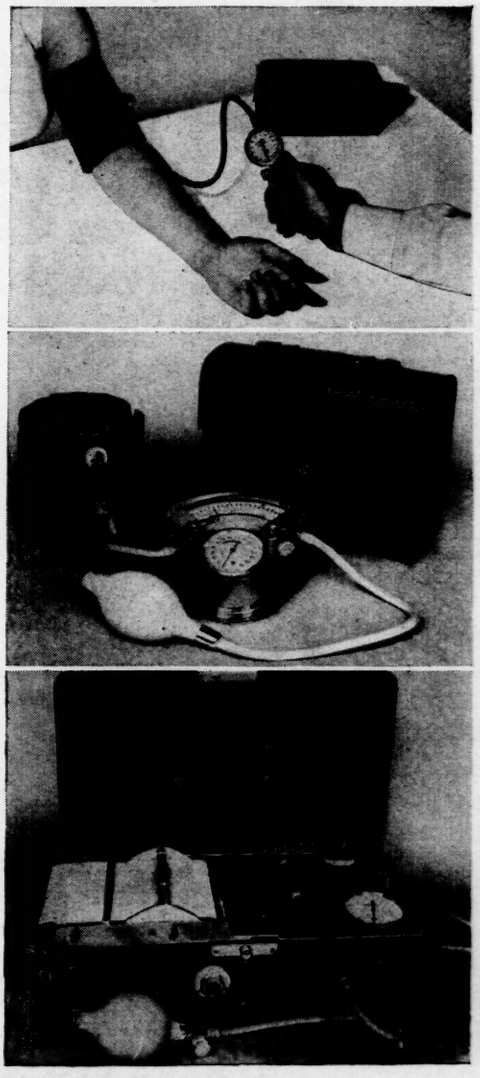
#2 Propper Oscillometer (Pachon)

Goes beyond blood pressure—provides the physician with further diagnostic and clinical information on peripheral vascular diseases—reveals impaired arterial circulation by completely objective, numerical *measurement* of vascular volume which can be compared with recognized and published norms for all parts of upper and lower extremities. Quickly verifies clinical picture indicative of certain diseases and provides a progressive record of the effect of the treatment. This, in addition to routine diastolic, systolic and mean blood pressures which can be obtained from the same instrument *without the use of a stethoscope.*

List Price **$87.50**

#3 Propper Oscillograph

For the physician who desires the ultimate in vascular diagnosis and case history. The Propper oscillograph gives *simultaneous* pulse readings of two extremities—and provides a permanent, written record of the test. For comparative studies and complete case histories the oscillograph is as important as the EKG. The most complete equipment—in one handy case—available only from Propper. For full information, write to:



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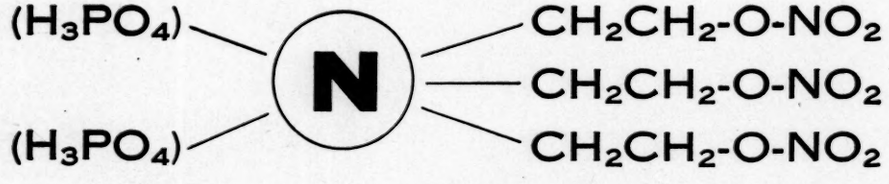

METAMINE is a new, *amino* nitrate, chemically unique, because its nitrate groups are linked through a nitrogen rather than through a carbon atom. The effective dose (2 mg.) of METAMINE is much smaller than those of other long-acting nitrates used to prevent angina pectoris.

METAMINE, newest of the long-acting coronary vasodilators, has the smallest effective dose: 2 mg. Taken routinely, METAMINE prevents attacks of angina pectoris or greatly diminishes their number and severity. Even during prolonged or excessive dosage, side effects are mild and infrequent. Tolerance and methemoglobinemia have not been reported.

The beneficial actions of METAMINE appear to affect the entire circulation, not just the coronary and myocardial vessels, reducing the work load and oxygen requirement of the heart and permitting a life of useful activity for the anginal patient who might otherwise become another cardiac cripple.

for prevention of angina pectoris

Numerous clinical and experimental studies since 1946 indicate that METAMINE is ideally suited for routine prevention of anginal attacks because of low (2 mg.) effective dose, prolonged action, and exceptional freedom from side effects and tolerance. Blood pressure is not altered. Finally, while slower to act than nitroglycerin, METAMINE "exerts a more prolonged and as good, if not slightly better, coronary vasodilator action . . ." (Melville, K.I., and Lu, F.C.: *Canadian M.A.J.*, 65:11, 1951.)

DOSAGE: To prevent angina pectoris, swallow 1 METAMINE tablet after each meal, and 1 or 2 tablets at bedtime. Full preventive effect is usually attained after 3rd day of treatment.

Thos. Leeming & Co. Inc.

155 EAST 44TH STREET, NEW YORK 17, N.Y.

The American Journal of Medicine

VOL. XVI FEBRUARY, 1954 No. 2

Psychosomatic Medicine—What Are We Talking About?

CURRENT references to psychosomatic medicine are often so formulated that confusion and failure of communication occur. Many terms are employed without reference to anything concrete and hence lack meaning in a medical context, or at least they do not have the same meaning to different persons. Much of the difficulty undoubtedly stems from a vocabulary which is inadequate, partly because so many traditional words in common use have not been satisfactorily defined. Consequently some "practical-minded" physicians are likely to consider the whole area exasperatingly nebulous, even though they may concede its importance; others become disturbed at what they see as the fostering of an alarming tendency to overlook life-threatening visceral lesions. There seems to be a real need to point out that it is possible to deal with psychosomatic medicine in a way which does not, in principle, involve any more mystery or vagueness than other approaches to medicine, and does not deny the significance of serious structural changes.

The following discussion attempts to outline an orientation which has been found to be useful and which avoids verbal traps. It is cast in the form of a dialogue because it seemed that this method emphasized some of the difficulties more effectively than a more conventional presentation, and that it avoided tedious circumlocution and indirect discourse. The purpose of writing it is to clarify some of the issues involved, not to try to convince anyone of the truth of any of the statements which are made in the name of psychosomatic medicine.

Many of the views expressed are derived in large part from the work of Halliday,[1] Wolf,[2] H. G. Wolff[3] and Guze, Matarazzo and Saslow[4] in which they are more extensively treated. The definition of *emotion* and the question of the existence of specific attitudes and emotions, different for each "psychosomatic" disease, are discussed by Grace and Graham.[5]

The conversation begins after the medical resident has completed a conventional case presentation to the "psychosomatic consultant."

RESIDENT: We asked you to see this patient because we think her disease is functional and we thought she should have a psychosomatic consultation.

CONSULTANT: Why did you think that?

R: Well, we can't find anything organic. All the laboratory tests and x-rays are negative.

C: I'm still not sure why you called me. So far all I know is that there are some diseases which she presumably does not have, since the diagnostic procedures which usually indicate their presence have not done so in this case.

R: As I said, we therefore concluded that the problem was functional so we thought it had an emotional basis—in other words, that it was psychogenic.

C: I didn't know that "psychogenic" and "functional" meant the same thing. I thought "functional" meant that there were disturbances in function although gross or microscopic inspection of organs and tissues showed no abnormalities. Tetanus is a functional disease.

R: But it has a physical cause. The kind of

[1] HALLIDAY, J. L. Principles of aetiology. *Brit. J. M. Psychol.*, 19: 367, 1941–43.

[2] WOLF, S. Experimental research into psychosomatic phenomena in medicine. *Science*, 107: 637, 1948.

[3] WOLFF, H. G. Life stress and bodily disease—a formulation. *Research Publ., A. Nerv. & Ment. Dis.*, 29: 1059, 1949.

[4] GUZE, S. B., MATARAZZO, J. D. and SASLOW, G. A formulation of principles of comprehensive medicine with special reference to learning theory. *J. Clin. Psychol.*, 9: 127, 1953.

[5] GRACE, W. J. and GRAHAM, D. T. Relationship of specific attitudes and emotions to certain bodily diseases. *Psychosom. Med.*, 14: 243, 1952.

functional disease I'm talking about has a psychic cause. And besides, some day somebody may discover histologic changes in tetanus.

C: Taking the last point first, the same may be said of any disease. And I wonder what you mean by a "psychic cause."

R: Well, that means that a disease is caused by some emotional upset, for instance. If a man's boss fires him and the man gets upset and gets sick, I'd call that a psychogenic disease.

C: But the boss is certainly a physical object, and his words are transmitted by physical sound waves which impinge on the patient's physical tympanic membrane, setting in motion a chain of events which leads eventually, via the auditory nerve, to certain physical events in his central nervous system. Perhaps something like that happened in the case of the woman you asked me to see.

R: Yes, she apparently got sick just after she learned that her husband was going out with another woman; she happened to see them on the street.

C: I think you will agree that the light waves coming from her husband and the other woman are likewise examples of physical stimuli. Perhaps we can say that there are certain kinds of physical stimuli which we tend to call "psychologic" to distinguish them from such things as arsenic or tetanus toxin or a bullet in the chest. It may be a little difficult to give a precise definition of "psychologic" in this connection but for practical purposes, within the framework of medicine, it usually suffices to think of them as those sensory stimuli which arise from the behavior of other persons. It is certainly not a new idea that, in general, diseases can be thought of as reactions of organisms to some stimuli or other. What I want to point out is that this concept applies to such diseases as your patient has.

You used the word emotional. Perhaps you will also agree that reactions to these "psychologic" stimuli, especially if the reactions are intense, are what we usually call "emotional reactions."

R: Do you mean that you wouldn't call any disease "psychogenic?"

C: If a "psychogenic disease" is understood to mean "a disease which is a reaction to psychologic stimuli," as we have just defined them, there seems to be no objection to the term.

But let's get back to the patient. You told me that the chief complaint was abdominal pain and that she also complains of palpitation. What do you know about the pain?

R: We think it's psychogenic because she says that it comes on now if her husband goes out without her in the evenings and, as I said, also because we didn't find anything organic.

C: Wait. We're getting two different questions mixed up. First, you told me something about the stimuli which provoke attacks of pain. You haven't told me what you think the basis of the pain is.

R: It's psychogenic or emotional or whatever you want to call it.

C: Yes, it occurs in response to stimuli which we have agreed to call psychologic. Another way of saying this is that it occurs in settings of life stress. This usually comes to the same thing, since the life stress to which most of our patients are exposed is not a matter of temperature extremes, oxygen deprivation or carrying heavy packs, for instance, but is rather psychologic, as we have just defined that word. This, however, is an etiologic question. Now I'd like to know what the anatomic and physiologic basis of the pain is. In other words, what is its pathogenesis?

R: I don't know what to say except to repeat that we think it's functional. I know we can't say that the pain is imaginary because if the patient says she feels it, then I suppose she does. I think it's just emotional.

C: Let's consider the palpitation. This also occurs in a setting of difficulty with her husband, i.e., it's psychogenic. But if I ask you for a physiologic explanation, you'll probably be able to say something more than a mere repetition of the word "functional."

R: Certainly. Her symptom of palpitation occurs when her heart beats faster or the stroke volume increases, and she becomes aware of the change in the heart's action. I don't see what you're getting at.

C: On the one hand you have one symptom (palpitation) occurring as part of an emotional response to life stress, and you can say something about the physiologic changes involved in it. On the other hand you have another symptom (abdominal pain) but this time you seem not to have asked yourself the same physiologic question.

R: Maybe it's due to some disturbance of intestinal motility. Is it very important to know?

C: Perhaps not in this case. We all know that

abdominal pain like hers, which has been intermittently present for several years without much change in character, and with the various other characteristics you have described, is, in fact, very unlikely to be an indication of any life-threatening disease, so that further diagnostic effort may, from the practical point of view, not be especially worth while.

R: We thought you might be able to make the diagnosis. You're the one who knows about psychoneurosis and things like that.

C: If I tried to make a diagnosis with respect to the abdominal pain, I'd have to do it the same way you did, by getting a description of the pain, doing a physical examination, and getting x-rays and various laboratory tests. Why did you mention "psychoneurosis"?

R: We hoped you'd tell us whether or not this patient is neurotic.

C: And by "neurotic" you mean . . . ?

R: A neurotic is a maladjusted person, somebody who gets upset very easily.

C: There has been a good deal of disagreement and confusion in the use of the words "neurosis" and "psychoneurosis." We don't need to go into all the possible definitions of those terms if we limit ourselves to what they mean as commonly used by most physicians. Isn't it a fair statement that a diagnosis of "neurosis" is usually made because of the presence of certain symptoms and behavior manifestations?

In other words, frequent visits to the doctor because of transitory pains, frequent weeping, a tendency to complain about life, attacks of tachycardia and sweating palms, worry about the significance of mild symptoms, failure to go out and get a job, are among the things which lead physicians to say that a person is "neurotic." Not all doctors use the word in the same way but this seems to be the kind of thing which is meant. Usually implied also is the requirement that the symptoms in question—chest pain, for instance—shall not be related to any serious structural disease. Didn't you have something more than this in mind?

R: When you're trying to find out whether some symptom is psychogenic, don't you have to decide whether the patient is neurotic?

C: Not if you *define* "neurosis" to mean the presence of the manifestations we've been talking about. A complete definition of this kind would be more complex, of course, but not different in principle. The frequent weeping and so forth are characteristics of the person in question but they may not be of much help in deciding about the etiology and pathogenesis of any particular symptom.

R: But if a symptom is psychogenic doesn't that mean that it's neurotic?

C: That amounts to changing the definition of "neurosis." One would then say that peptic ulcer was a neurosis because it is so closely related to life stress and emotional disturbance. Some people do call it a neurosis, which of course is all right as long as the meaning of the word is clear.

R: Some authors doubt that peptic ulcer is a psychosomatic disease, because they say that a lot of their patients aren't neurotic.

C: This is a return to the first definition of "neurosis" we talked about, and I'm sure that in that sense the statement is true. Many persons with peptic ulcer are undoubtedly free of the symptoms and signs we said we could use to make the definition of "neurosis," but that is not the same thing as saying that the disease is not "psychogenic." It is interesting to know whether or not persons with asthma, ulcer, and so forth, are neurotic, in the first sense, but it is not the crucial question. It's something like asking whether they have red hair, or high intelligence or some other characteristic.

Since we're discussing peptic ulcer, I'd like to ask you whether you'd call that a "functional" or "organic" disease.

R: I suppose it would usually be called "organic." I guess you mean that a disease can be psychogenic, whether it's organic or functional.

C: Exactly. Another point that comes up sometimes is in connection with the use of the term "somatic." Doctors who are interested in psychologic medicine are often urged not to "overlook the somatic component."

R: As a matter of fact, all these symptoms and signs we've been talking about must be a reflection of "somatic" processes—like the rapid heart rate in the woman with palpitation, for instance.

C: In general, wouldn't you say that emotional behavior involves various sorts of physiologic processes, some in the hollow viscera, some in the skeletal muscles, and so forth? A depressed patient who weeps constantly is certainly weeping somatic tears, for instance. A paranoid killer uses his somatic finger to pull the trigger of his gun.

R: I wonder what you'd say about psychotic

patients who have disordered thinking. Is that bodily, too?

C: Well, in the first place the only way we can know about the thinking at all is by having some kind of behavior (which is to say, some kind of somatic processes) to inform us. The behavior may consist of movements of the organs of speech, so that the patient tells us what he's thinking, or it may be something else.

R: I have thoughts that I don't tell anybody about, and I'm sure other people do, too.

C: But don't you suppose that there must be some relation between your thinking and events in your central nervous system? Could you have thoughts without a body?

R: Even if I could, I don't know how anybody else would ever find out about them; so I guess, from the standpoint of the other person, it would be just the same as if I didn't.

C: In other words, all we can deal with in medicine is events of some sort or another which occur in the patient's body.

R: There's another thing that bothers me a little. It seems to me that all this emphasis on psychosomatic medicine sometimes leads to disaster. I remember one man, for instance, who came in complaining of weight loss, anorexia and some indefinite epigastric distress. They didn't find anything on the work-up, which included gastrointestinal x-rays, and referred him to the psychiatric clinic. A few weeks later he turned out to have cancer of the stomach.

C: I see that a diagnostic error was made but I'm not sure what it has to do with psychosomatic medicine.

R: Since nothing organic was found they decided the illness was psychogenic and thought he ought to have psychotherapy.

C: We decided earlier that even if you come to the conclusion that a patient's illness is psychogenic, you have not made a diagnosis. In other words, you still don't necessarily understand the anatomic and physiologic basis of the symptoms and signs. In the case you mention, however, there doesn't even seem to be any particular reason to regard the illness as psychogenic.

R: Well, he seemed to be sort of depressed so a diagnosis of depression was made, I guess.

C: I suspect that what really happened was that somebody went through the following chain of thought: (1) X-ray and other laboratory tests show no significant abnormalities, (2) therefore the illness is psychogenic and (3) therefore no fatal or crippling structural changes will develop. It should be clear from what we've said that neither (2) nor (3) follows from (1), and that there is no necessary connection between (2) and (3).

The real source of the error here was not overemphasis on psychosomatic medicine but rather overreliance on the diagnostic efficiency of the x-ray, combined with the illogical reasoning just mentioned.

It is, of course, true that there is a loosely defined entity known as "depression," which seems to me just as physiologic as any other disease although we know relatively little about the nature of the physiologic changes. The symptoms to which these changes give rise may, in fact, be very similar to those associated with cancer of the stomach. Even if this man went so far as to say that he knew that he felt depressed, his symptoms and signs should have been carefully evaluated in an effort to define, in so far as possible, their physiologic and anatomic basis.

R: I do remember that somebody told me that he got sick right after he had a lot of trouble at home. That may be one of the reasons he was sent to the psychiatry clinic. You don't think that cancer of the stomach is a psychosomatic disease, do you?

C: I haven't any idea. That is a strictly empirical question to be decided by future research. The relation between the life stress and the cancer in this man may be pure coincidence. Maybe none of his principal symptoms had anything to do with the trouble at home, since we know nothing of the evidence in this case.

In the light of our discussion, I wonder what you think of the practice of referring patients for psychotherapy because they have "vague" or "bizarre" complaints.

R: I suppose that, as a matter of fact, a lot of vague and bizarre complaints are psychogenic but I guess there's no reason to think that they must necessarily be. I remember one man who was about to be referred to a psychiatrist because of unexplained abdominal pain. He then developed weight loss and fever, however, and it was decided to do an exploratory laparotomy. It turned out that he had retroperitoneal sarcoma.

I imagine even you will agree, though, that some signs and symptoms are almost always psychogenic, and furthermore not reflections of serious structural changes.

C: Yes. That is analogous to saying that

vomiting and diarrhea of explosive onset and brief duration, occurring simultaneously in all members of a family, are probably due to ingestion of contaminated food and not associated with serious structural changes.

R: I have another question. You wouldn't say that life stress is *the* cause of things like ulcer or essential hypertension, would you? Aren't there other factors?

C: Certainly. There is nothing that can be said to be *the* cause of any disease. To take an obvious example, the tubercle bacillus is not the only cause of pulmonary tuberculosis; the characteristics of the lung are also involved.

An important point comes up here. We have talked about the stimulus to a disease (etiology) and the physiologic and anatomic changes concerned (pathogenesis). There is at least one other question, which is, Why does this person react in this way? You might, for instance, wonder why one man gets an ulcer when he is fired from his job, another in the same circumstances goes off on a prolonged drinking spree, and a third goes out and gets another job without developing any significant symptoms. The answer involves knowing something about the state of the organism exposed to the stimulus. You would like to know to what other stimuli the man is exposed and how he is reacting to them; what his genetic attributes are; what things have happened to him in the past.

Such considerations are nothing new in medicine. We know, for instance, that a man who has been previously inoculated with killed typhoid bacilli will, if he later ingests pathogenic ones, not react in the same way as another man who has never received typhoid vaccine.

R: Asking about the nature of the organism which is reacting to these various stimuli sounds as if it had something to do with the idea of personality types in various diseases, like ulcer or asthma. Do you think there's anything to that?

C: There's a good deal of disagreement about it. Apart from its theoretical interest, the problem may sometimes have some immediate clinical importance. You might want to know whether you could find out from a patient or his family things about his feelings and behavior which would help you decide what disease he has.

R: Do you think that if a man has epigastric pain, for instance, with negative or equivocal x-ray findings, you might get some diagnostic help by talking to him to find out whether he is the "ulcer type"?

C: Possibly. The same question is sometimes asked in cases of diarrhea when the possibility of chronic ulcerative colitis is raised. Some people think that there are differences in the behavior and attitudes of persons with different diseases, and others disagree.

R: So there may be some chance that talking with a patient, in addition to asking the usual questions about the symptoms, may help to make the kind of physiologic diagnosis we've been talking about?

C: Yes, but we're a long way from being able to do that with much certainty. The conventional history, physical examination and laboratory tests are much more reliable diagnostic methods.

R: Well, this is an interesting way of looking at things. I don't know that I'm entirely convinced but I'll think about it. I imagine a lot of people wouldn't agree with you. How do you know your way is right?

C: There may be a better way. All I can say is that the one I've been talking about seems to provide a way to ask concrete questions and get concrete answers, without getting involved in purely verbal disagreements. In addition, it may, because it keeps separate questions separate, help to avoid diagnostic errors like the one you mentioned in the case of carcinoma of the stomach.

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Clinical Studies

Comparative Effects of Aspirin, ACTH and Cortisone on the Acute Course of Rheumatic Fever in Young Adult Males*

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SINCE the original communication of Hench et al.[1] concerning the effect of adrenal cortical hormones on acute rheumatic fever many reports have appeared indicating that treatment with cortisone and ACTH favorably alters the acute course of rheumatic fever. These investigations have usually compared the effects of the hormone preparations with previous experience with other modes of treatment. Since the progress and prognosis of acute rheumatic fever is difficult to evaluate in a given individual, it would seem necessary to evaluate various methods of therapy concurrently by studying large groups of patients who are similar and selected in an unbiased manner, and to include a control series of untreated patients. The American Council on Rheumatic Fever through its Sub-committee on Criteria and Standards has devised a study to compare the effects of treatment with cortisone, ACTH and aspirin on the course of acute rheumatic fever. The present report concerns the evaluation of such treatment in young adult males and was conducted in co-operation with and as part of the larger study of the American Council on Rheumatic Fever.‡

METHODS AND DESCRIPTION OF STUDY

From January, 1951, to June, 1952, all male airmen admitted to this hospital with a tentative diagnosis of rheumatic fever were assigned to a special study ward for confirmation of the diagnosis. If they met the diagnostic criteria established for this study (Table I) and certain signs of activity§ (Table I) were present on the initial day of therapy, they were included in the study and assigned consecutive study numbers.‖

Treatment for each patient was arbitrarily assigned according to a predetermined schedule enclosed in a serially numbered envelope which corresponded to the patients' assigned study number.¶ The schedules of treatment are presented in Table II. Aspirin was administered orally every four hours during the first two days and every six hours for the remainder of the treatment period. Cortisone was administered intramuscularly in a single daily dose. ACTH** was injected intramuscularly in equally divided

‡ The authors are indebted to Dr. David D. Rutstein, Chairman, Miss Marjorie Bellows, Statistician, and the principle investigators of the Cooperative Rheumatic Fever Study for advice and the protocol used in this study.

§ The presence of either one major manifestation or two of the three following minor manipulations: elevated sedimentation rate, fever, or prolonged P-R interval, was considered a sign of activity.

‖ During the first six months of the present study another drug (3-hydroxy, 2-phenylcinchoninic acid (HPC)) was also used as therapy. Thirty-four patients received such therapy. The results, comparing these thirty-four patients to thirty-four patients from the present aspirin-treated series, have been reported elsewhere.[2]

¶ These envelopes were prepared and sealed prior to the beginning of the study by Miss Marjorie Bellows.

** Acthar (ACTH) was kindly furnished by the Armour Laboratories, Chicago, Ill.

* From the Medical Service, USAF Hospital and the Streptococcal Disease Laboratory, Francis E. Warren Air Force Base, Wyoming, and the Department of Preventive Medicine, School of Medicine, Western Reserve University, Cleveland, Ohio. This investigation was conducted under the sponsorship of the Commission on Acute Respiratory Diseases and the Commission on Streptococcal Diseases, Armed Forces Epidemiological Board, and was supported by the Offices of The Surgeons General, Departments of the Army and Air Force, Washington, D. C.

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doses every six hours. All patients were treated for forty-two days. Three weeks after the cessation of treatment if any patient still met the criteria for rheumatic activity, treatment was reinstituted with the same drug and dosage but continued for only four weeks. All patients received a diet containing less than 2 gm. of sodium per day for the first four weeks of treatment. Three gm. of potassium chloride were administered orally each day during the six weeks of treatment. To eradicate the streptococcal carrier state all patients received penicillin, 600,000 units in oil, on the day of admission to the study and every three days thereafter for four injections. Following the course of penicillin each patient received 1 gm. of sulfadiazine daily for the remainder of the study period. The patients were kept at bed rest for a minimum of nine weeks.

TABLE I

DIAGNOSTIC CRITERIA FOR ADMISSION TO STUDY*

Major manifestations:

1. Carditis—as evidenced by any one of the following:
   (a) Development of a significant (organic) systolic murmur or an aortic diastolic murmur under observation
   (b) Change in heart size, by standard x-ray film (more than 15%)
   (c) Pericarditis—friction rub or effusion
   (d) Congestive failure in the absence of other causes
2. Polyarthritis—pain and limitation of active motion or tenderness in two or more joints
3. Chorea
4. Subcutaneous nodules
5. Erythema marginatum

Minor manifestations:

1. Fever—temperature above 100.3°F. rectally at least twice in a twenty-four-hour period, or above 101.3°F. rectally at any time in the course
2. Elevated sedimentation rate—15 mm./hr. or over (Wintrobe, corrected)
3. Preceding streptococcal infection—by throat culture, or antistreptolysin "O" titer of 200 units or greater, or a history of definite sore throat with fever during preceding two to four weeks
4. Abnormal P-R interval—a value of .22 seconds or more
5. History of rheumatic fever—a reliable history involving same criteria as herein described or evidence of rheumatic heart disease

* The presence of either two major manifestations or of one major and two minor manifestations was regarded as sufficient for diagnosis of rheumatic fever.

Each patient was examined daily by one of three physicians during the six-week period of treatment and for three weeks thereafter. Insofar as possible a patient was examined by the same physician during the period of observation and the patients were assigned in such a manner that each physician was given an equal distribution of patients among the treatment groups. Rectal temperatures were obtained every four hours. Sleeping pulse, blood pressure determination and weight were recorded daily. Electrocardiograms were obtained daily for the first three weeks, every other day for the next six weeks and at weekly intervals thereafter until the patient was discharged. Erythrocyte sedimentation rates were done by the Wintrobe method three times weekly during the first three weeks of treatment and the week following treatment; at all other times they were done once weekly unless they were found to be abnormal in which case they were done three times weekly until normal. Teleroentgenograms were taken on admission to the study and weekly thereafter for nine weeks. Serum potassium and plasma CO_2 determinations were performed at weekly intervals in the hormone-treated patients during therapy. Eosinophil counts were done according to the method of Randolph[3] in the hormone-treated patients three times weekly during the first week and at weekly intervals during the last five weeks of therapy. Serum for antistreptolysin "O" titers and throat cultures for β-hemolytic streptococci were obtained every ten days for the first nine weeks. The presence of C-reactive protein* was determined by the method

TABLE II

SCHEDULES OF TREATMENT

Drug	Daily Dose (mg.)	Day of Treatment
Aspirin.....	65/pound body weight*	1 and 2
	44/pound body weight	3–7
	33/pound body weight	8–42
Cortisone.....	300	1
	200	2–5
	100	6–21
	75	22–35
	50	36–42
ACTH.....	120	1–4
	100	5–7
	80	8–14
	60	15–21
	40	22–35
	20	36–42

* Maximum daily dose 9.7 gm.

* The authors are indebted to Dr. Maclyn McCarty of the Rockefeller Hospital for the immune rabbit serum used in determining the presence of C-reactive protein.

of Anderson and McCarty[4] in three serum specimens obtained from each patient at seven- to ten-day intervals; the first of the serial specimens was obtained during the last week of therapy. After the first nine weeks follow-up examinations were made at monthly intervals.

TABLE III
COMPARABILITY OF THE TREATMENT GROUPS AT THE TIME THERAPY WAS INSTITUTED

	Aspirin	Cortisone	ACTH
Number of patients	61	45	42
Average age at onset of rheumatic fever	20.1	19.6	19.6
Average day of illness	8 5	8.7	10.2
Median day of illness	6	7	7
Major manifestations:			
Per cent of patients with			
1. Carditis	14.7	15.5	9.5
(a) Development of or change in murmur	11.5	8.9	7.1
(b) Change in heart size	0	0	0
(c) Pericarditis	1.6	4.4	0
(d) Congestive failure	1.6	2.2	2.4
2. Polyarthritis	88.5	95.6	95.2
3. Chorea	0	0	0
4. Subcutaneous nodules	0	0	0
5. Erythema marginatum	1.6	0	2.4
Minor manifestations:			
Per cent of patients with			
1. Fever	83.6	82.2	85.7
2. Abnormal erythrocyte sedimentation rate	83.0	86.4	95.2
3. Abnormal P-R interval	37.7	35.6	35.7
Rheumatic fever history			
Per cent of patients with			
1. Personal history of rheumatic fever	19.7	31.1	16.7
2. Personal history of heart murmur	9.8	11.1	7.1
3. Family history of rheumatic fever	16.4	2.2	11.9
Per cent of patients with rheumatic heart disease	1.6	6.7	7.1

Physical examinations and histories were obtained to ascertain whether or not any patient had had an intervening streptococcal infection, renewed rheumatic activity or any change in physical status. Complete blood count, urinalysis, electrocardiogram, sedimentation rate, throat culture and a serum specimen for antistreptolysin determination were obtained at the monthly follow-up. Chest x-rays were repeated at six and twelve months.

COMPARABILITY OF THE THREE TREATMENT GROUPS

One hundred fifty-two patients met the established criteria for admission to the study. Sixty-three were treated with aspirin, forty-five received cortisone and forty-four received ACTH.*

Two aspirin-treated patients and two ACTH-treated patients developed toxic symptoms which necessitated discontinuance of therapy. These patients have been excluded from the analysis. Comparison of the remaining patients in the three treatment groups at the time treatment was instituted is presented in Table III. The day of illness when treatment was started ranged from two to fifty-two in the aspirin-treated group, from two to thirty-two in the group receiving cortisone and from two to ninety-six in the ACTH-treated group. Except for two patients, one each in the aspirin-treated and ACTH-treated groups, all patients were treated within thirty-two days of the onset of their illness; 85 per cent of the patients in each group were treated within the first fourteen days of the onset of their illness. Major and minor manifestations were present with similar frequency among the three groups except for a greater incidence of previous attacks of rheumatic fever among the patients who received cortisone. In addition, the percentage of aspirin-treated patients who had evidence of rheumatic heart disease on admission to the study was smaller than that in either of the other two groups.

RESULTS

The effect of the three drugs on joint symptoms is presented in Figure 1. There was rapid subsidence of joint symptoms in all three groups, but pain disappeared most rapidly in those patients treated with aspirin. On the third day of therapy only 35 per cent of the aspirin-treated patients complained of joint symptoms whereas 60 and 70 per cent of the ACTH and cortisone-treated patients, respectively, had such symptoms. Redness, swelling and immobility of the affected joints cleared most rapidly in the aspirin-treated patients although in all groups such signs of joint involvement had usually disappeared by the fifth or sixth day of treatment. During the remainder of the treatment period arthralgia and tenderness were the chief findings in those patients who continued to have symptomatic joints after initiation of therapy. In all three groups symptoms and signs continued to appear in

* During the time that HPC was used as therapy, treatment allocation was arranged so that one-third of the patients would receive HPC, one-third would receive aspirin, one-sixth would receive cortisone and one-sixth would receive ACTH. When HPC was no longer used, the allocation of treatment was arranged so that the remaining patients would be equally placed among the aspirin, cortisone and ACTH schedules. Therefore, there were a larger number of patients included in the aspirin schedule.

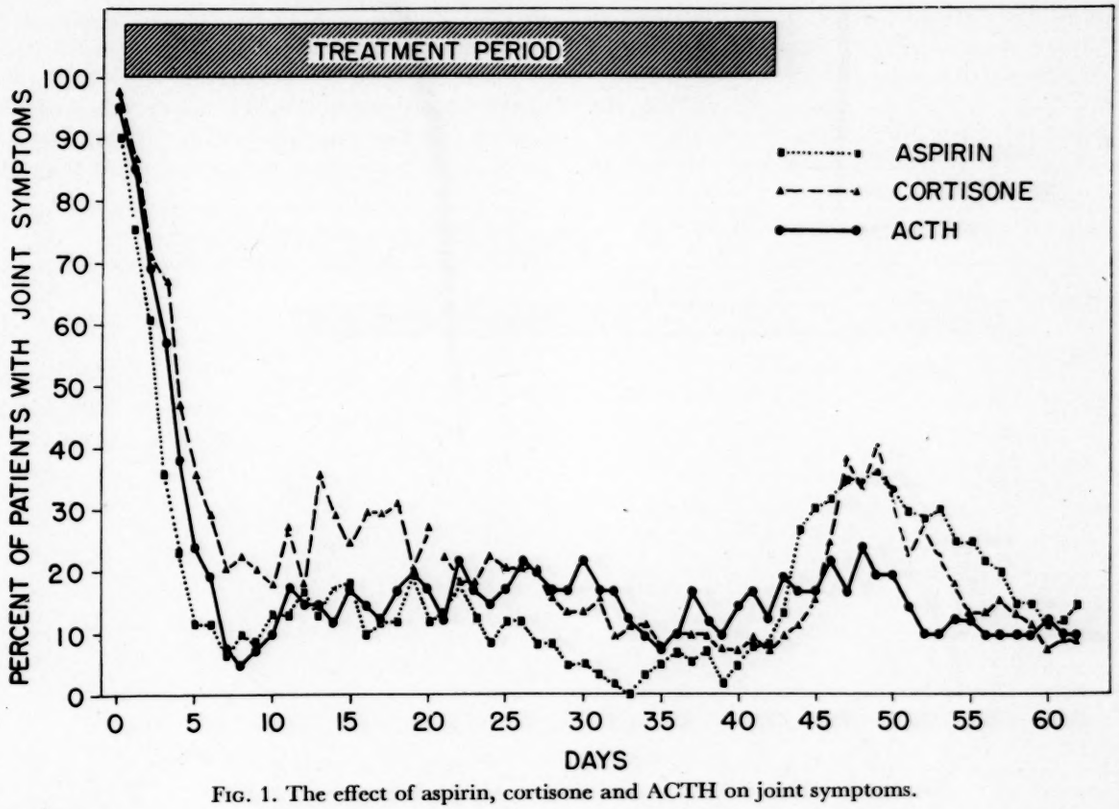

FIG. 1. The effect of aspirin, cortisone and ACTH on joint symptoms.

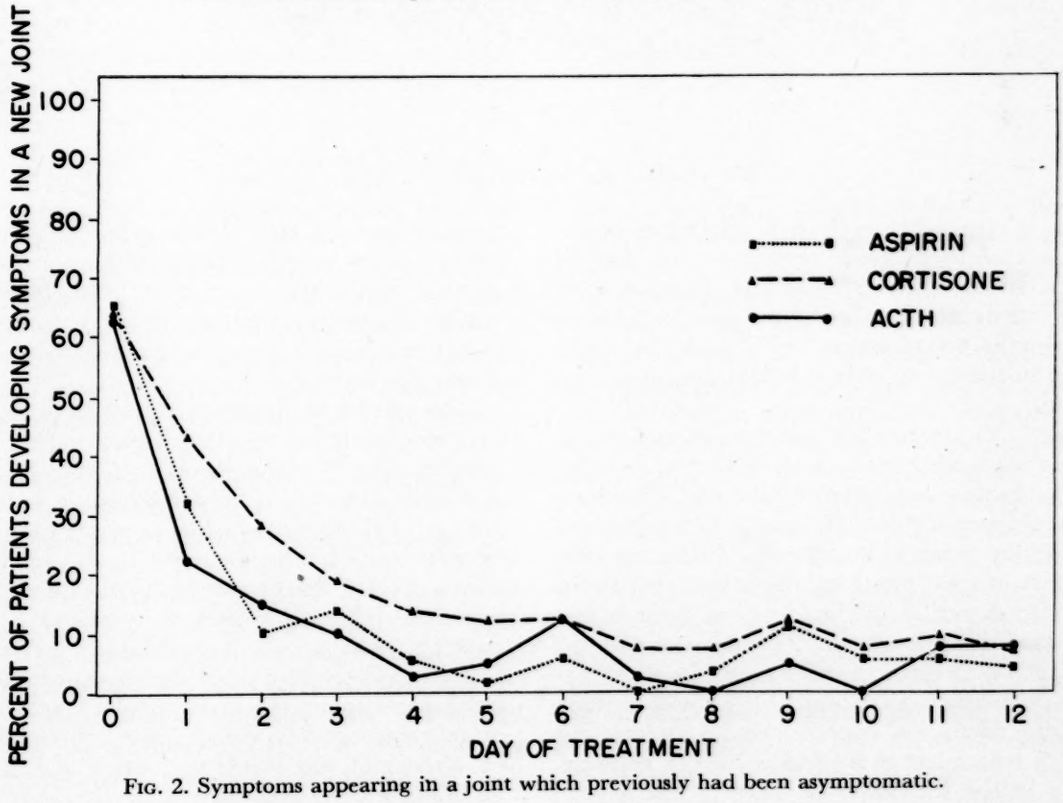

FIG. 2. Symptoms appearing in a joint which previously had been asymptomatic.

joints which were not involved at the onset of treatment. (Fig. 2.) From the foregoing data it would appear that aspirin most effectively controlled joint symptoms and signs during the period of drug administration. Following cessation of therapy there was a marked rebound or

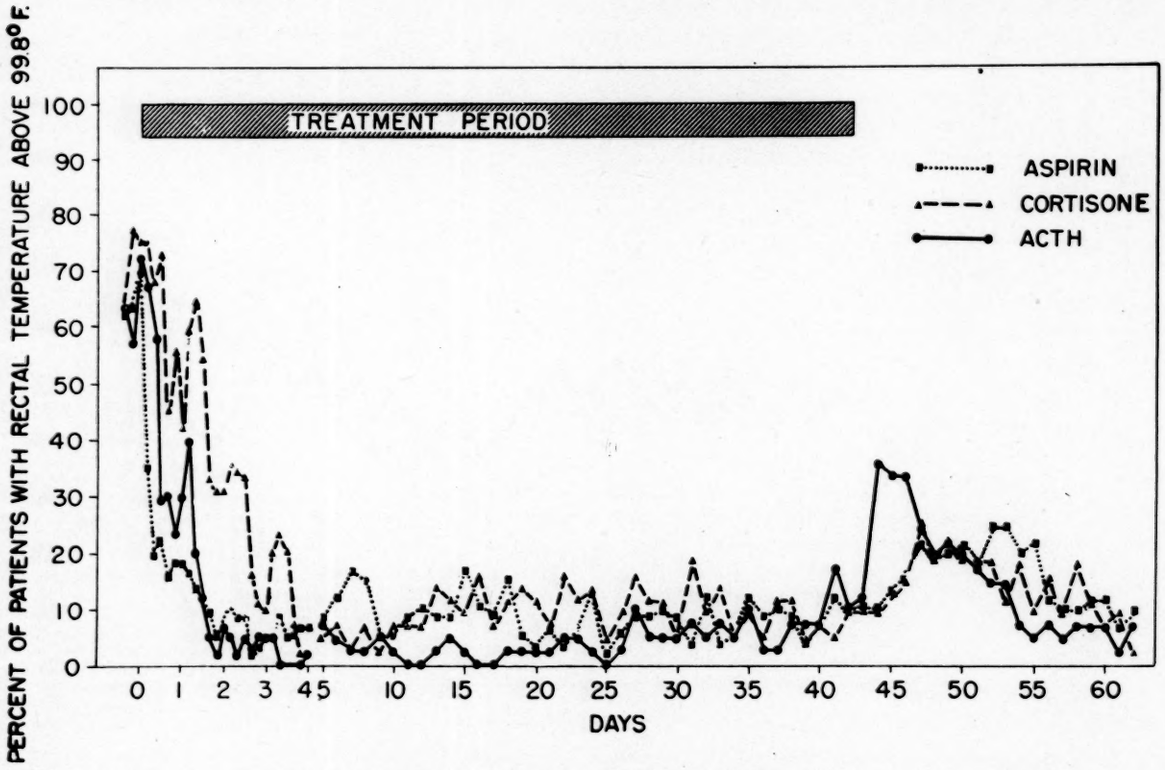

FIG. 3. The effect of aspirin, cortisone and ACTH on fever.

return of symptoms in the aspirin and cortisone groups and to a lesser degree in the ACTH group. In all three groups the signs of joint involvement after treatment was completed were occasionally more severe than were those observed in the same patient before treatment was started.

Figure 3 indicates the per cent of patients in each group with fever (100°F. or above, rectally) before, during and after treatment. The incidence of fever at four-hour intervals is presented for the day prior to and for the four days after the start of treatment; for the remainder of the observation period the incidence of fever is presented at daily intervals. The decrease in the incidence of fever was more rapid in those patients receiving aspirin and ACTH than in those receiving cortisone. Within four hours from the start of treatment there was a 50 per cent decrease in the incidence of fever in the aspirin group. Four days after the start of treatment the groups were indistinguishable in this respect and remained so for the remainder of the treatment period, although ACTH appeared somewhat more effective than the other drugs. After the end of therapy there was more rapid reappearance of fever in the ACTH group than in the other two treatment groups. Although the pattern of reappearance of fever after treatment varied among the three groups, the percentage of patients in each group who exhibited this was about the same.

The pattern of incidence of abnormal erythrocyte sedimentation rates varied among the three groups. (Fig. 4.) The increase in the incidence of abnormal sedimentation rates in the cortisone and ACTH groups during therapy may have been related to the decrease in dosage of the drugs. When therapy was discontinued, there was little rebound among the cortisone-treated patients, which may be explained by the already relatively high incidence of abnormal rates in this group at the sixth week. Seven weeks after treatment was discontinued the incidence of abnormal sedimentation rates was similar among the three groups.

The per cent of gain or loss in average weight compared to the average weight at the time treatment was initiated is presented in Figure 5. The weight loss in the aspirin group during the first week may be related in part to the anorexia, nausea and occasional vomiting and in one patient sixteen days after treatment was discontinued. Two cortisone-treated patients developed erythema marginatum on the twentieth and forty-second day of treatment and two patients developed such lesions eight and ten days after therapy ceased. In the ACTH

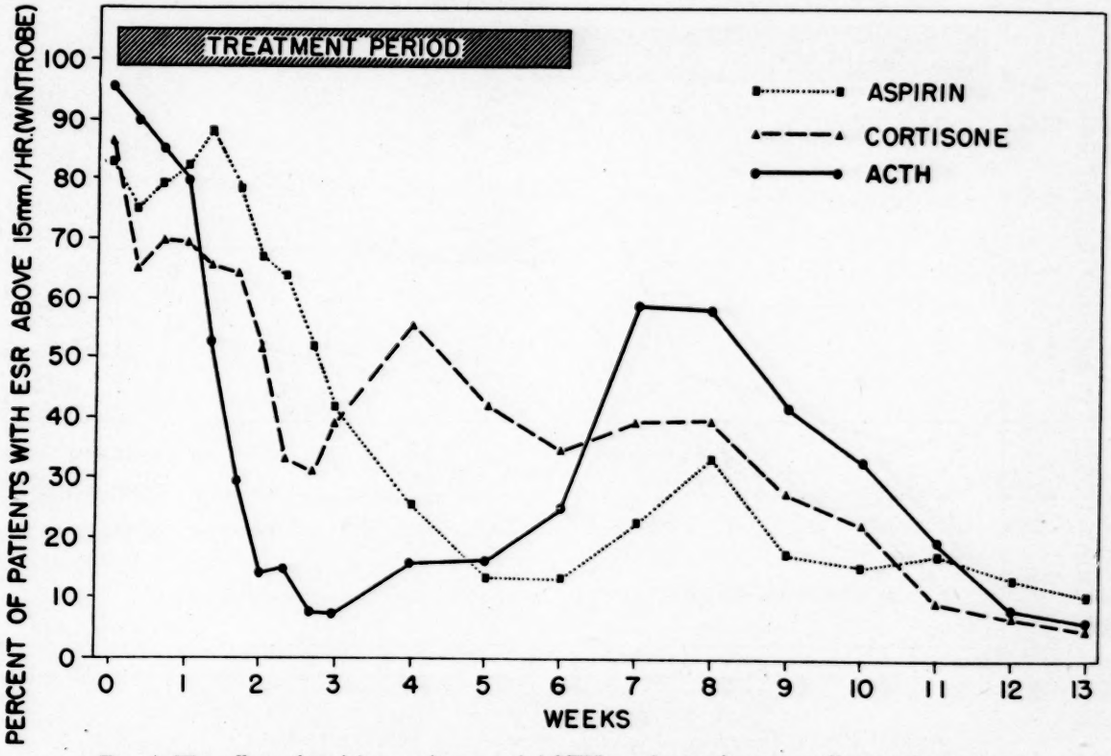

FIG. 4. The effect of aspirin, cortisone and ACTH on the erythrocyte sedimentation rate.

which occurred frequently in these patients. The rapid weight gain observed in all groups between the fourth and sixth weeks may be due to the amount of food consumed since the diet during this time was much more palatable than the low-sodium diet; however, in the hormone-treated patients increased retention of water was undoubtedly responsible for some of the gain in weight.

The duration, disappearance and reappearance of erythema marginatum varied considerably among the patients but there was no marked difference in the several groups. The one patient who received aspirin and had erythema marginatum at the start of treatment had no skin lesions after the first day of therapy. Such lesions persisted for four days in the ACTH-treated patient in whom they were present at the start of therapy. Erythema marginatum appeared in three aspirin-treated patients on the third, thirtieth and thirty-first day of treatment group two patients developed skin lesions on the eighteenth and twenty-sixth days of treatment and none developed erythema marginatum for the first time after therapy.

Subcutaneous nodules were not observed in any of the patients who received aspirin. One cortisone-treated patient developed a nodule which was first observed twenty-five days after the end of treatment and which persisted for seven days. A single nodule, first observed in an ACTH-treated patient on the eighteenth day of treatment, disappeared on the fortieth day of treatment.

Definite chorea was not present in any patient. One patient, on the seventh day after ACTH therapy had been completed, developed a generalized clonic convulsion which persisted for three to four minutes. Following this episode he continued to have, with gradually decreasing frequency, involuntary movements of extremities and facial muscles. These movements were

not typically choreiform. A complete neuropsychiatric evaluation revealed a marked hysterical pattern in this patient.

Three patients with signs of cardiac failure at the start of therapy, one in each treated group, improved rapidly. The failure was mild in each of the patients and all signs had disappeared in two days in the aspirin-treated patient, in three days in the cortisone-treated patient and in seven days in the ACTH-treated patient. Cardiac failure occurred in two other patients, both in the aspirin-treated group, twenty-two and seventy-six days after therapy was discontinued. Each of these patients was retreated with aspirin and these, except for institution of a low-sodium diet and mercurial diuretics in one patient, required no additional therapy. The pericardial friction rubs present at the start of therapy persisted for two and four days in the two patients treated with cortisone and for six days in the one aspirin-treated patient. Precordial pain of the type usually accompanying pericarditis was present in approximately 10 per cent of the patients in each group when treatment was started. None of these patients showed other evidence of pericarditis by physical examination, roentgenograms or electrocardiograms. The duration of pain was approximately five days in all patients irrespective of the form of treatment.

The incidence of tachycardia* and of bradycardia as determined by measurement of the ventricular rate recorded on the electrocardiograms is presented in Figure 6. When the incidence of tachycardia is compared to that of fever (Fig. 3), it can be seen that there is a fairly close correlation between the two. However, the reappearance of a rapid ventricular rate preceded the reappearance of fever in the ACTH and cortisone groups and appeared to be a more sensitive indication of decreased dosage than was the fever. Bradycardia appeared earlier and in a larger percentage of the hormone-treated patients than in the aspirin-treated patients. It persisted longer, however, in the aspirin-treated patients. Bradycardia has been observed during the treatment of rheumatic fever with these three drugs[1,5,6] and also in the absence of treatment.[6] The significance of this is not clear although Bywaters and Dixon[5] regarded its presence in their hormone-treated patients as additional evidence of effective dosage.

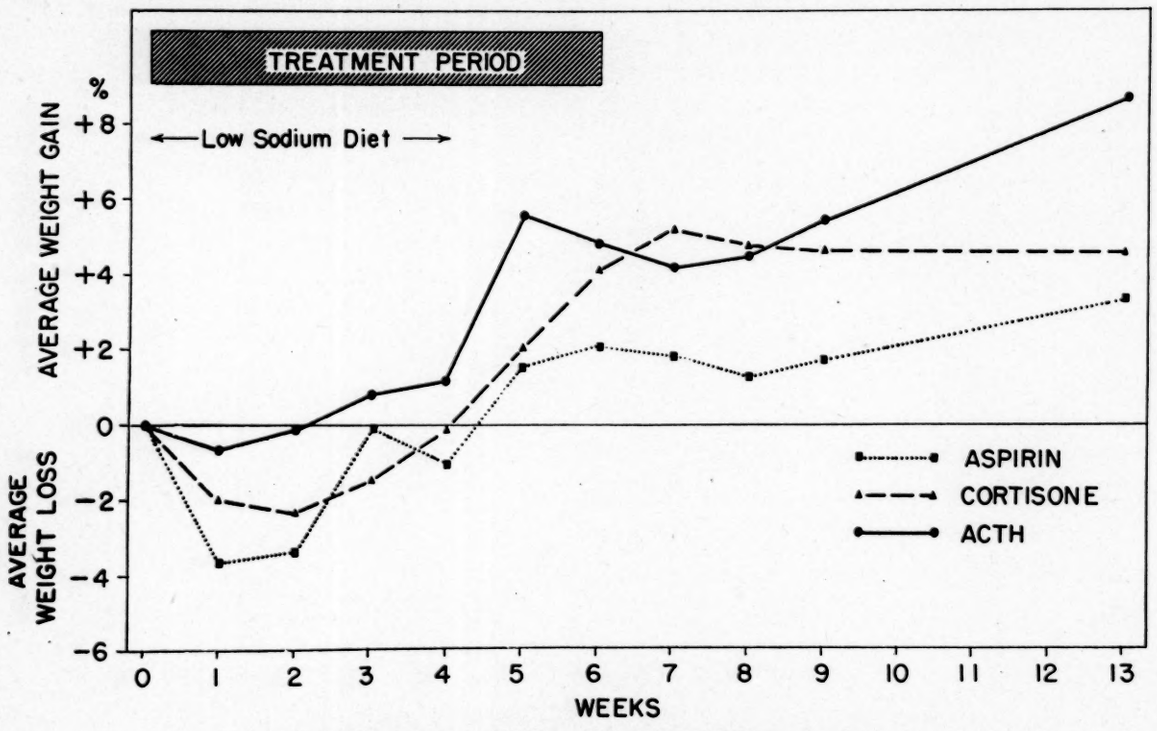

FIG. 5. The effect of aspirin, cortisone and ACTH on weight.

Weekly roentgenograms revealed a slight

* Ventricular rates above 100 were rarely encountered and for the purposes of comparison tachycardia has been defined as a rate of 90 or greater.

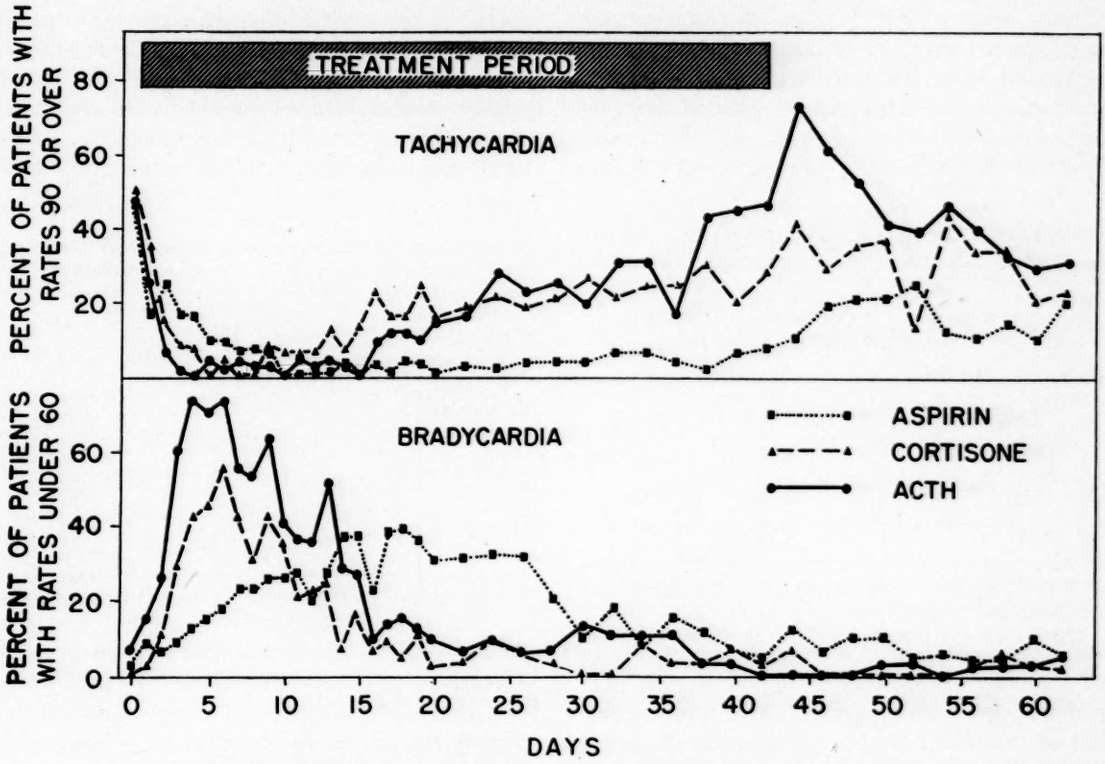

FIG. 6. The effect of aspirin, cortisone and ACTH on the ventricular rate.

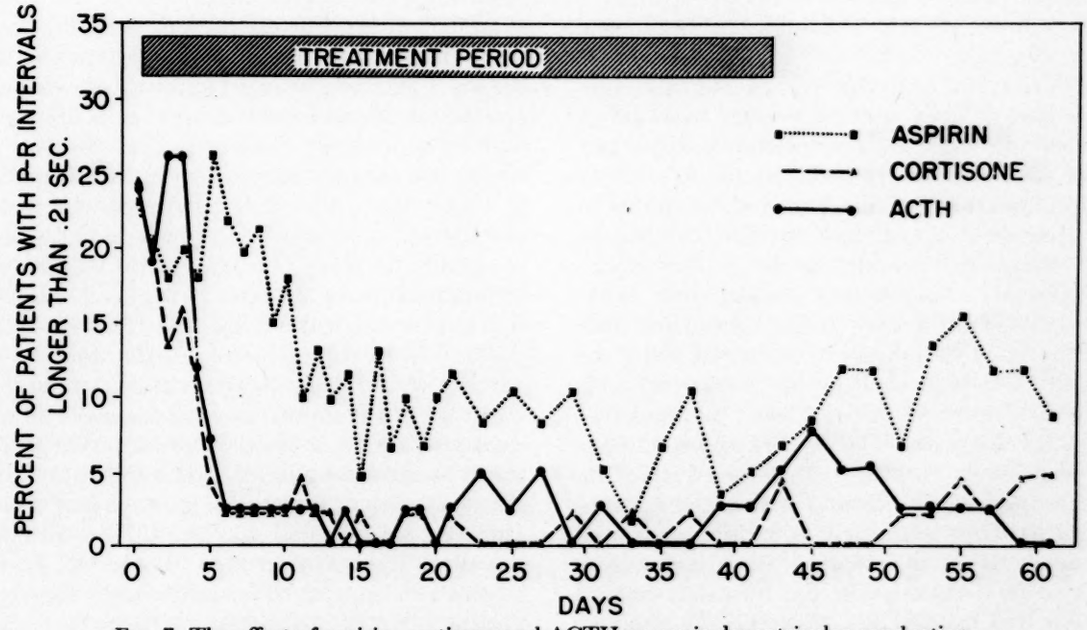

FIG. 7. The effect of aspirin, cortisone and ACTH on auriculoventricular conduction.

difference among the groups in relation to change in heart size. When the low salt diet was discontinued after the fourth week of therapy, the hormone-treated patients showed an increase in heart size which appeared to be directly related to their increased weight gain.

TABLE IV
OCCURRENCE OF MURMURS AMONG PATIENTS WHO HAD NO MURMUR AT THE START OF TREATMENT*

Interval after the Start of Treatment (wk.)	Aspirin (34 patients)		Cortisone (31 patients)		ACTH (24 patients)	
	No.	Per cent	No.	Per cent	No.	Per cent
9	16	47.1	5	16.1	4	16.7
18	13	38.2	10	32.2	8	33.4

* Including patients with rheumatic heart disease if a new murmur appeared.

When treatment ended, however, the average heart size for the groups returned to the pre-treatment level. At the end of the nine weeks' period of observation the average heart size of all three groups was essentially equal to that at the onset of treatment. Between 11 and 15 per cent of the patients in each of the groups had a 5 per cent or greater reduction in heart size during the nine weeks' period. Five per cent of the patients in both the ACTH and salicylate groups had a 5 per cent or greater increase in heart size during the same period as did 9 per cent of the cortisone-treated patients.

Approximately 50 per cent of the patients in each treatment group had an abnormality in A-V conduction (usually prolongation of the P-R interval) at some time during their acute illness. Abnormalities appearing for the first time after the start of treatment occurred with the same frequency in each group. However, as is shown in Figure 7, the duration of abnormal P-R intervals varied. The ACTH and cortisone-treated patients returned to normal during the first few days of treatment whereas the aspirin-treated patients continued to exhibit abnormal P-R intervals much longer. Within the normal range of A-V conduction the hormone-treated patients had consistently shorter P-R intervals and the P-R intervals of patients with bradycardia tended to be shorter in those receiving hormones. After the end of treatment there was an increase in the number of abnormal P-R intervals in all treatment groups and approximately 2 per cent of the patients in each group exhibited an abnormal conduction for the first time during this period.

The evaluation of murmurs heard during acute rheumatic fever is extremely difficult. Their significance in terms of future valvular disease usually can be assessed only in retrospect. Therefore a detailed analysis of the intensity, duration, location, etc., of those murmurs heard during the period of observation is not included in the present discussion. The incidence of valvular disease in these patients fourteen months following their acute illness will be the subject of a later report. For the present, only the occurrence of murmurs nine and eighteen weeks after the start of therapy in relation to the presence or absence of a murmur at the start of treatment will be considered (Tables IV and V). The patients who are represented by the data appearing in these two tables had murmurs which were considered to be related to the observed episode of rheumatic fever. Therefore, individuals with rheumatic heart disease have been excluded unless a new murmur appeared. There was little difference, in respect to the appearance or persistence of murmurs, between those patients with a history of rheumatic fever and those who were experiencing their initial attack. When only those patients who developed a murmur during therapy are considered, it is apparent that at eighteen weeks there was no difference among the three treatment groups (Table IV). In contrast, there appears to be a difference among the groups when persistence of murmurs is analyzed (Table V). The significance of these results can be determined only by further study. Only five patients had persistence at eighteen weeks of aortic diastolic murmurs which appeared during treatment. Three had received aspirin, the re-

TABLE V
OCCURRENCE OF MURMURS AMONG PATIENTS WHO HAD A MURMUR AT THE START OF TREATMENT*

Interval after the Start of Treatment (wk.)	Aspirin (27 patients)		Cortisone (13 patients)		ACTH (16 patients)	
	No.	Per cent	No.	Per cent	No.	Per cent
9	22	82.0	7	53.8	10	62.5
18	22	82.0	4	30.8	14	87.5

* Excluding patients with rheumatic heart disease.

maining two had been treated with ACTH. Aortic diastolic murmurs were noted transiently during treatment in two additional aspirin-treated patients, one cortisone-treated patient and four ACTH-treated patients. Apical mid-diastolic murmurs had disappeared by the end of nine weeks in eighteen patients equally distributed among the treatment groups. At the present time, with a long-term follow-up available in only a limited number of patients, it appears that the murmurs present during the acute illness in the aspirin-treated group tended to remain although murmurs disappeared in a few instances. Among the patients treated with ACTH and cortisone, murmurs, not heard during the acute illness, often appeared during convalescence or later. This trend is apparent in Table IV.

Toxic or side-effects of therapy were apparent in some degree in all of the aspirin or ACTH-treated patients and in 75 per cent of those patients receiving cortisone. Tinnitus (97 per cent) and nausea (51 per cent) were the most frequent symptoms associated with aspirin intake but were usually absent or mild after the first week of therapy. Moonface and acne tended to be more severe among the patients receiving ACTH in contrast to those receiving cortisone. In general, none of the side-effects were severe, with the following exceptions. The appearance of acute psychoses on the twenty-eighth day of treatment in two ACTH-treated patients necessitated discontinuance of therapy. The mental status of each of these patients was normal after approximately three months of psychiatric care. One additional patient had an exacerbation of duodenal ulcer during ACTH therapy but it was not necessary to stop the drug. Two aspirin-treated patients developed severe epistaxis associated with hypoprothrombinemia and therapy was discontinued. An additional patient receiving aspirin developed hyperventilation and a severe respiratory alkalosis but with discontinuance of therapy made a prompt recovery and treatment was reinstituted at a smaller dosage level.

There was a significant lowering of the total circulating eosinophils in all the patients receiving hormonal therapy. Normal eosinophil counts usually reappeared, however, at the end of three weeks of therapy in the cortisone group and a week later in the ACTH group.

Rebound, Relapse and Retreatment. During the three-week period after the end of treatment fifty-one aspirin-treated patients, forty-three cortisone-treated patients and thirty-eight ACTH-treated patients showed some manifestation of rheumatic activity other than a heart murmur. The incidence of these manifestations is shown in Table VI. The only marked dissimilarity among the three groups is a lower incidence of abnormal erythrocyte sedimentation rates in the aspirin group. Joint symptoms reappeared earlier in the ACTH and aspirin-treated groups than in the cortisone-treated group. For example, joint symptoms reappeared within three days in one-half of the ACTH and aspirin-treated patients who had such recurrences but five days elapsed before a like number of the cortisone-treated patients had recurrences.

TABLE VI

PERSISTENCE OR APPEARANCE OF SYMPTOMS AND SIGNS AFTER THERAPY WAS DISCONTINUED

Treatment	Joint Manifestations				Abnormal ESR				C-reactive Protein				Fever after Therapy*		Other†	
	At End of Therapy		After Therapy		At End of Therapy		After Therapy		Last Week of Therapy		After Therapy					
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Aspirin.....	6	10	38	62	8	13	22	36	16‡	27	28	46	28	46	18	30
Cortisone.....	3	7	25	56	14	31	28	62	12	27	26	58	21	47	10	22
ACTH.....	6	14	18	43	9	21	28	67	7	17	25	60	19	45	6	14

* Rectal temperature above 100°F.

† Abnormal A-V conduction, erythema marginatum or pericarditis.

‡ One unknown.

None of the ACTH-treated patients had reappearance of joint symptoms later than ten days after cessation of therapy, while in the other two treatment groups joint symptoms reappeared up to seventeen days after treatment. The average duration of joint symptoms was seven days in the aspirin-treated group compared to five days in the ACTH and cortisone-treated groups.

In general, if an abnormal sedimentation rate or C-reactive protein was present during the last week of therapy the rebound was more severe. In all groups there were a few instances in which cessation of treatment in the presence of an abnormal sedimentation rate, C-reactive protein and joint symptoms did not result in a severe rebound, although at least one of the manifestations usually became more severe. In the groups as a whole there was no apparent difference in the severity of the symptoms and signs which returned, although the duration of the abnormalities was slightly longer in the aspirin-treated group.

After treatment was discontinued significant murmurs appeared for the first time in one aspirin-treated patient, one ACTH-treated patient and six cortisone-treated patients. However, all but the one aspirin-treated patient had had murmurs during the treatment period although the murmurs were inconstant at the time and were not considered to be significant. In only two of these patients, both in the cortisone-treated group, was the relapse severe, although all of the patients had evidence of a return or increase in severity of at least two of the manifestations considered in Table VI. In only one of the two patients was the relapse severe enough to result in retreatment. The significance of the rebound or relapse in terms of future rheumatic heart disease will have to await the results of long-term follow-up. At the present time there is not sufficient evidence to indicate that the relapse or rebound *per se* was a significant factor in determining the ultimate status of these patients.

At the end of the three weeks' period of observation three patients in the aspirin-treated group and one each from the other two groups still met the criteria for activity, as here defined, and were retreated. The two hormone-treated patients and one of the aspirin-treated patients had polyarthritis, pericarditis, elevated erythrocyte sedimentation rate and fever. One patient who had received aspirin had polyarthritis, fever, elevated sedimentation rate and a prolonged P-R interval. The other aspirin-treated patient had an elevated sedimentation rate and a prolonged P-R interval. Three other patients from the aspirin-treated group were retreated 84, 89 and 146 days, respectively, after the original course of treatment had concluded. No evidence of an intercurrent streptococcal infection was noted in these patients and each had evidence of continued rheumatic activity during the period between therapy. Thus a second course of therapy was administered to six aspirin-treated patients, one ACTH-treated patient and one cortisone-treated patient. No patient required a third course of therapy.

COMMENTS

The present series of patients provided an excellent opportunity for assay of the comparative value of the three drugs now in most common use in the treatment of acute rheumatic fever in young adults. The age range encompassed was fairly narrow, a large proportion of the patients was experiencing a first attack of rheumatic fever and treatment was started early after the onset of symptoms. The last fact is of particular importance in the evaluation of any form of therapy of rheumatic fever. Of course, it is entirely possible and not unlikely that in many patients irreversible changes had occurred before the symptoms of rheumatic fever were apparent.

In the dosages and routes of administration employed, there appeared to be no marked difference among the three drugs in their effect on the acute course of rheumatic fever. In the absence of an untreated group it is not possible to state that the duration of illness was altered. Previous studies have indicated that aspirin treatment does not alter the duration of the illness.[6,7] Experience with cortisone and ACTH, utilizing a comparable control group, has not previously been reported.

That aspirin affords symptomatic relief in rheumatic fever has been generally accepted but that it has any effect on carditis is still a matter of controversy.[6–9] A divergence of opinion has also arisen about the effect of ACTH or cortisone on carditis and the incidence of persistent rheumatic heart disease.[10–13] In the present study aspirin gave the promptest symptomatic relief. The response to cortisone was slowest although oral administration of this drug might have resulted in more rapid amelioration of symptoms and signs. ACTH and cortisone ap-

peared to shorten the duration of abnormal A-V conduction although not preventing its appearance. Whether or not the seemingly favorable effect of ACTH and cortisone on the presence of heart murmurs during the period of administration of these drugs will be reflected in a decreased incidence of valvular disease awaits the results of a long-term follow-up. The later appearance of murmurs among the hormone-treated patients raises the important question of whether or not these murmurs would have appeared if treatment had been continued longer. It was demonstrated, however, that murmurs appeared during therapy with the hormones and that these murmurs persisted.

The return of symptoms and signs after discontinuance of therapy and, as was frequently observed, their reappearance coincidental with a reduction in dosage has been noted by others.[14,15] In patients receiving ACTH or cortisone an explanation for the occurrence of this phenomenon, usually termed rebound to denote a temporary period of abnormality followed by a spontaneous remission, has been advanced by Bunim,[14] and Ziegra and Kuttner.[15] In their opinion it is related to the point in the natural course of the disease at which therapy is discontinued. If this point is after the clinical manifestation would have subsided naturally, there would be no evidence of a relapse or rebound, although occasionally a "laboratory rebound" might occur. In general, the data from the present study would tend to substantiate this explanation. There are certain points, however, which are at variance with this theory. Since in a disease as variable as acute rheumatic fever it would be unlikely that all patients would have a similar duration of illness, the presence of some abnormality in almost all the patients after the end of treatment is difficult to explain. Also, in the two hormone-treatment groups there was a larger percentage of patients with C-reactive protein and abnormal sedimentation rates after cessation of therapy. This might indicate that ACTH and cortisone, while suppressing the inflammatory process actually delayed complete resolution. Rheumatic activity might continue, therefore, after cessation of treatment. Thus the late appearance of murmurs in the two hormone-treated groups would be explained.

SUMMARY

A comparison was made of the effects of treatment with aspirin, cortisone and ACTH in 148 young adult males with acute rheumatic fever. Sixty-one of the patients received aspirin; forty-five received cortisone and forty-two received ACTH.

Fever, joint pain and objective evidences of joint involvement were relieved most promptly with aspirin; ACTH was more effective in this respect than cortisone. Apart from the promptness of relief, there was little difference in the three drugs in their effects on the symptoms of acute rheumatic fever.

The pattern of response of the erythrocyte sedimentation rate was different in each of the three therapy groups. Cortisone and ACTH treatment resulted in shortening the duration of abnormal auriculoventricular conduction; however, this might be a result of a specific action on conduction. Other indices of the effects of the drugs on carditis are presented but their final interpretation must await the results of a long-term follow-up. In each group, however, new murmurs appeared and persisted while the patients were receiving ostensibly full therapeutic dosages of the drugs.

A clinical and/or laboratory relapse or "rebound" occurred in almost all of the patients in each group after cessation of therapy. This relapse subsided spontaneously in all except six aspirin-treated patients, one cortisone-treated patient and one ACTH-treated patient. A second course of therapy was administered to these patients.

Toxicity and/or side-effects associated with use of the three drugs occurred in all the aspirin and ACTH-treated patients and in 75 per cent of the cortisone-treated patients. In only four patients, two each in the aspirin and ACTH-treated groups, were these severe enough to necessitate discontinuance of therapy. Acute psychoses developed in two ACTH-treated patients.

Since an untreated control group of patients was not included in this study, it is not possible to determine what effect, if any, these three drugs had on the duration or residuals of acute rheumatic fever. It is clear, however, that the over-all effect of each of the drugs leaves much to be desired in the treatment of acute rheumatic fever and that adequate therapy for this disease is not presently available.

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Observations on the Antirheumatic and Physiologic Effects of Phenylbutazone (Butazolidin) and Some Comparisons with Cortisone*

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PHENYLBUTAZONE† (butazolidin®) has been recently introduced as a drug for the treatment of rheumatoid arthritis and allied disorders. A number of reports indicate that in various musculoskeletal disorders the drug exerts therapeutic effects comparable to those elicited by cortisone and corticotropin.[1–4] The purpose of the present study was to compare the antirheumatic and other physiologic effects of phenylbutazone in man with those produced by cortisone and corticotropin.

The physiologic disposition of phenylbutazone has been described elsewhere in detail.[5] At plasma levels of 50 to 150 mg. per L. (levels within the range of therapeutic concentration) approximately 98 per cent of the drug is bound to plasma proteins. Because of the affinity of phenylbutazone for plasma proteins, the concentration of drug in plasma is appreciably higher than in organ tissues (Table 1) and about one-third of a single dose of the drug is localized in plasma. The concentrations of phenylbutazone in saliva and gastric juice are negligible. The level of drug in the synovial fluid of an arthritic patient was found to be 80 mg. per L. as compared with a plasma concentration of 145 mg. per L.

† Phenylbutazone was supplied through the courtesy of Geigy Pharmaceuticals, New York, N. Y. To preclude possible irregularities in absorption of tablet preparations, the drug was made up for oral administration in gelatin capsules, each containing 200 mg. of powdered drug.

Phenylbutazone is rapidly and completely absorbed from the gastrointestinal tract, the peak plasma level of the drug being reached usually within two hours after oral administration. When administered by the intramuscular route the peak plasma level is not usually attained for six to ten hours due to localization of the drug at the site of injection. (Fig. 1.) Consequently a more rapid therapeutic effect should be obtained by giving phenylbutazone orally than intramuscularly; the main advantage in giving the drug intramuscularly may be to reduce nausea and vomiting in certain cases.

TABLE 1
DISTRIBUTION OF PHENYLBUTAZONE IN HUMAN TISSUES*

Tissue	Concentration of Phenylbutazone (mg./kg.)
Plasma	115
Plasma ultrafiltrate	2.3
Adrenals	80
Heart	55
Spleen	37
Kidney	70
Lung	78
Muscle	45

* Patient received 800 mg. phenylbutazone orally for several days prior to death, and received the last dose of 200 mg. about twelve hours before death. The tissues were removed for analysis within three hours postmortem.

Negligible amounts of phenylbutazone are excreted as such in the urine since the drug is

* From the Laboratory of Chemical Pharmacology, National Heart Institute, National Institutes of Health, Department of Health, Education, and Welfare, Bethesda, Md.; Institute of Physical Medicine and Rehabilitation, New York University, Bellevue Medical Center, New York, N. Y.; and the Research Service, Third (New York University) Medical Division, Goldwater Memorial Hospital, New York, N. Y. This investigation was supported in part by the Public Health Research Institute of the City of New York.

almost completely metabolized in the body. The rate of metabolic transformation in man is relatively slow, averaging 20 per cent per day. Considerable variation in this rate is observed however, ranging from 10 to 35 per cent per day

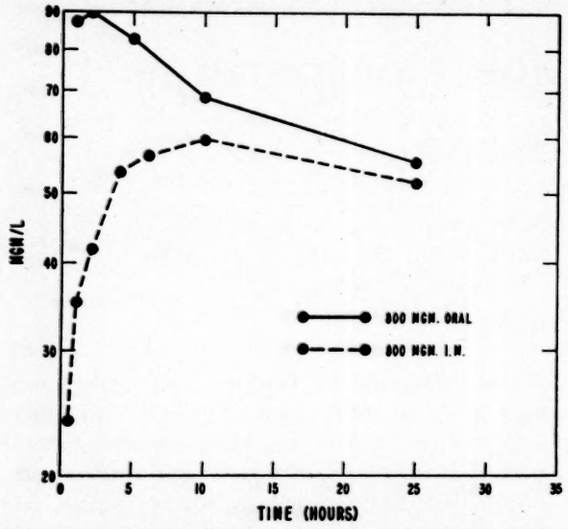

FIG. 1. Plasma levels of phenylbutazone after a single oral and intramuscular dose of the drug to the same subject.

(Fig. 2) with most of the values lying between 15 and 25 per cent.

On repeated oral dosage the drug accumulates in the body and there is a progressive increase in plasma concentration, which reaches a plateau on the third or fourth day and thereafter is constant from day to day. The plateau level differs widely from person to person and ranges from 60 to 150 mg. per L. (Fig. 3) with 75 per cent of the values falling between 90 and 130 mg. per L.; these differences reflect mainly individual differences in the rate of metabolism of the drug. Because of the slow biotransformation of the drug it makes little difference in the plateau plasma level whether the total daily drug is administered in single or divided doses. It is generally believed, however, that the incidence of nausea and vomiting is lessened by giving the dose in divided doses.

Patients with compensated Laennec's cirrhosis appear to metabolize the drug as readily as normal subjects. This observation suggests that, at least in this type of liver disease, the biochemical mechanism which metabolizes phenylbutazone is not affected.

Phenylbutazone behaves in an unusual manner in that plasma levels of the drug fail to increase commensurately with increasing doses but tend to approach a limiting concentration. Thus subjects on a daily dosage schedule of 1,600 mg. achieve plasma levels that are only about 10 per cent higher than those obtained on an 800 mg. schedule. The value of this limit-

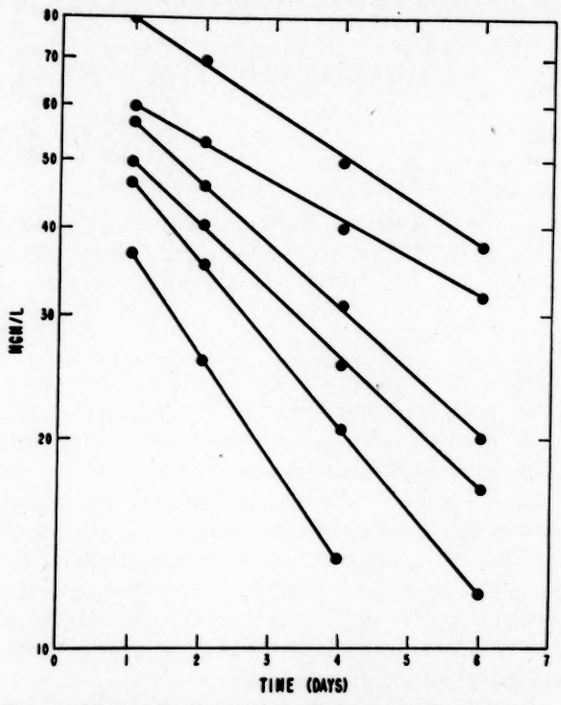

FIG. 2. Plasma levels of phenylbutazone after administration of a single 800 mg. dose of the drug to various subjects.

ing concentration varies considerably among different individuals. (Fig. 4.) In explaining this phenomenon the factors of absorption and excretion are not involved since negligible amounts of the drug are excreted in urine or feces. The possibility of increased storage in tissues without a corresponding elevation in plasma levels has been shown to be unlikely. It is probable that there is a marked increase in the rate of metabolic transformation at the elevated plasma levels which are achieved shortly after the administration of large doses of the drug. Preliminary experiments indicate that at plasma levels of about 200 mg. per L. the apparent velocity constant for the metabolic transformation of the drug is considerably higher than at levels of 100 mg. per L.

While this unusual phenomenon requires further study, it is suggested that one of the factors which explains the more rapid metabolism of phenylbutazone on the higher dosage schedule is the degree of its binding on plasma

proteins. At a plasma level of 100 mg. per L. 98 per cent of the drug is bound to plasma proteins and only a small proportion of the drug is available in an unbound state to the biochemical mechanisms which metabolize it. However, at plasma levels in the range of 250 mg. per L. only 88 per cent of the drug is bound to plasma proteins. A proportionately larger fraction of the drug is therefore available in free form and metabolic transformation proceeds at an accelerated pace.

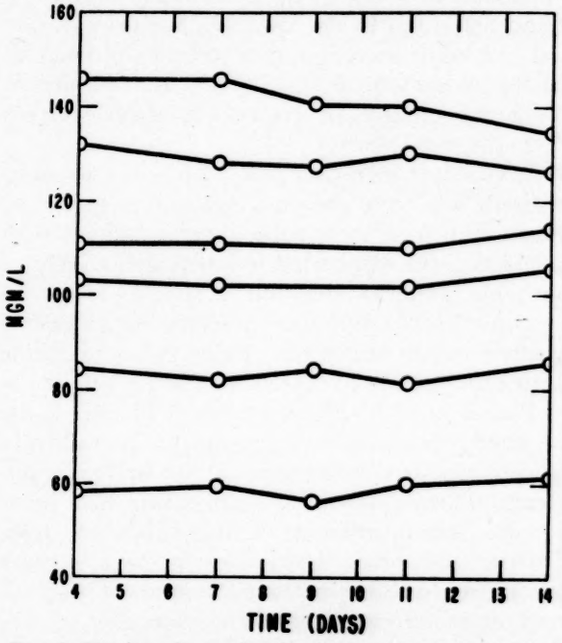

FIG. 3. Plateau plasma levels of phenylbutazone during the oral administration of 800 mg. of the drug daily.

There are marked species differences in the rate of metabolic transformation of the drug. For instance the dog, rabbit, rat and guinea pig metabolize the drug about fifteen times faster than does man. This makes it difficult to apply toxicologic and pharmacologic results obtained with animals directly to man.

MATERIALS AND PROCEDURES

The antirheumatic effects of phenylbutazone were studied in eighteen hospitalized patients who were severely disabled rheumatoid arthritics with active inflammation of the joints. All antirheumatic medication had been discontinued and for two weeks prior to the period of study they were examined periodically to evaluate the degree of articular inflammation.

Following the initial period of observation, the patients were given placebos for seven days, four capsules daily with meals. Fluid output and body weight were recorded daily. In six patients eosinophil counts, urinary excretion of sodium, potassium, chloride and 17-ketosteroids were also measured.

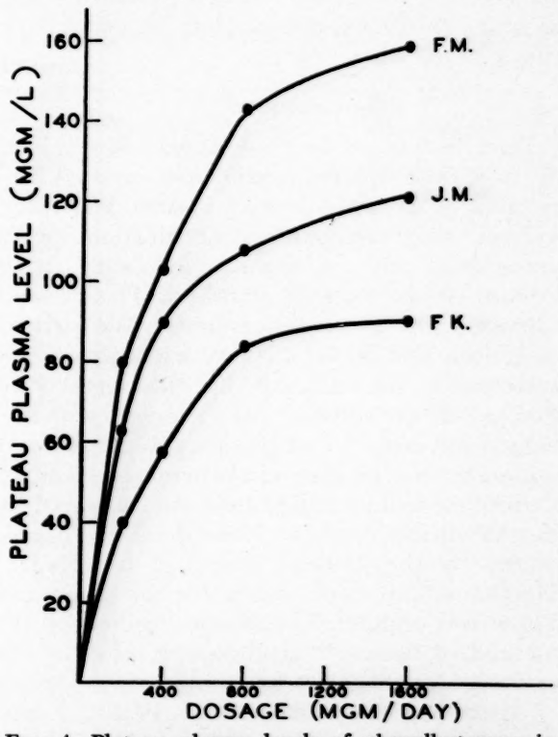

FIG. 4. Plateau plasma levels of phenylbutazone in three subjects on successive dosage regimens of 200, 400, 800 and 1,600 mg. of the drug daily. Each point represents the plateau plasma level achieved for each dosage regimen.

After the period of placebo administration the patient was either given phenylbutazone or continued on placebos; neither the observers nor the patient knew at the time which was being given.

The daily dose of phenylbutazone was 800 mg. given in gelatin capsules, each containing 200 mg. of powdered drug; two capsules were given with breakfast, one with lunch and one with dinner. Duration of therapy varied from eight to 105 days. After discontinuance of phenylbutazone therapy cortisone was administered to twelve patients in whom active inflammation recurred. This drug was given in initial doses of 100 mg. daily for ten days to two weeks, with gradual reduction thereafter to maintenance levels of from 25 to 75 mg.

Ten non-arthritic subjects without heart,

liver or kidney disease were also given phenylbutazone in therapeutic doses in order to study in greater detail the urinary excretion of electrolytes, and the effect on circulating eosinophils and blood volume. Fifty-nine additional patients were given phenylbutazone for periods of one week to six months without detailed study in order to obtain information regarding side effects of the drug.

METHODS

Phenylbutazone in plasma was determined by a simple spectrophotometric method developed in this laboratory.[5] Plasma and urine sodium and potassium concentrations were determined with a flame photometer using lithium as an internal standard. Plasma and urinary chlorides were measured by the method of Wilson and Ball.[6] Urinary excretion of 17-ketosteroids was assayed by the method of Pincus.[7] Blood volume was measured with P^{32} tagged red cells,*[8] and plasma volume and red cell mass were calculated from hematocrit values. Erthrocyte sedimentation rate was measured by the Wintrobe method. Eosinophils were estimated by the method described by Thorn.[9] Platelet counts were made by the Rees and Ecker wet technic;[10] capillary fragility by the method of Brown;[11] prothrombin time by the one-stage method;[12] prothrombin consumption as described by Weiner and Wald;[13] antithrombin by a new simplified technic.[14]

CLINICAL RESULTS

Antirheumatic Effects of Phenylbutazone in Rheumatoid Arthritis. The antirheumatic effects were evaluated according to the criteria of the American Rheumatism Association[15] and are presented in Table II. Eight patients showed major improvement (grade II response). In these the antirheumatic response to the drug followed the pattern observed with cortisone therapy. Within twenty-four hours, as a rule, there was reduction of stiffness, followed in the next few days by a diminution of articular tenderness and pain on motion. Resolution of synovial effusion was the last to occur, taking place over two to three weeks. The improvement of the arthritic manifestations was accompanied by a sense of well-being, an increase in appetite and energy, and decrease in fatigue.

Nine of the patients showed only minor improvement (grade III response), with a slight diminution of signs of rheumatoid activity and considerable relief of pain. One patient failed to improve (grade IV).

The erythrocyte sedimentation rate was measured in seven patients showing a grade II response. It fell in six instances but only in one did the sedimentation rate return to normal. In the group who showed grade III–IV improvement the change in erthrocyte sedimentation rate was variable.

Comparisons with Cortisone. Five of the eight patients who had shown a grade II response to phenylbutazone were subsequently treated with cortisone and responded equally well. Eight of the ten patients showing a grade III or IV response to phenylbutazone were subsequently treated with cortisone. Only one of these responded better to cortisone. (Table II.)

Plasma Levels of Phenylbutazone. Plasma levels of phenylbutazone were measured periodically during therapy in sixteen of the arthritic patients. Plasma samples were taken just prior to the administration of the morning dose. During the first three to four days plasma levels progressively increased, reached a plateau, and thereafter were constant from day to day for a given individual. The plateau level differed widely from patient to patient, ranging from 69 to 142 mg. per L. (Table II.) These values lie in approximately the same range as those previously obtained with normal subjects.[5]

Five of six patients who had a grade II response had plateau plasma levels in excess of 100 mg. per L. On the other hand five of ten patients who showed only a minor response also had levels over 100 mg. per L. In this limited series of patients it was not possible to correlate plasma levels with clinical response.

On discontinuance of phenylbutazone in seven arthritic patients plasma levels declined slowly at a rate which averaged 15 per cent per day, which is comparable to the rate previously observed in normal subjects.[5]

The effect of increasing the dose on the plasma level was studied in three rheumatic patients (B. W., C. C. and F. B.). The three patients were put on successive dosage regimens of 800, 1,200 and 1,600 mg. of phenylbutazone daily. Each schedule was maintained for a period of at least two weeks. Blood samples were taken each day just prior to the morning dose. On

* We are indebted for the blood volume studies to Dr. Leo Meyer of the New York University Medical Division, Goldwater Memorial Hospital, New York, N. Y.

each dosage regimen plasma levels reached a plateau in three to four days and then remained relatively constant until the dose was increased. Table III shows the plateau plasma levels achieved on the various dosage schedules. It is seen that with increasing doses of phenylbutazone, plasma levels failed to increase in a proportional manner and tended to reach a limiting concentration. The plasma level rose only slightly when the daily dose was increased from 800 mg. to 1,600 mg. and was not accompanied by any additional clinical response.

These observations suggest that there is little advantage to be gained, as a rule, in administering large doses of phenylbutazone. Further evidence of this was obtained in a study of seventy patients with various types of arthritis and allied diseases, half of whom received 400 mg. of the drug daily and the other half twice this dose.* The average plateau plasma level on the 400 mg. schedule was 93 mg. per L. while the average level for the higher dose was only 107 mg. per L., or 15 per cent higher.

The Side Effects of Phenylbutazone. A number of side effects, some of which are similar to those following administration of cortisone or corticotropin, were observed among the eighty-seven patients given phenylbutazone.

The development of edema of varying severity was observed in about one-third of the

TABLE II

CLINICAL RESULTS WITH PHENYLBUTAZONE IN EIGHTEEN CASES OF RHEUMATOID ARTHRITIS; COMPARISONS WITH CORTISONE

Subject	Age and Sex	Duration Arthritis (yr.)	Stage Arthritis*	Duration Treatment (days)	Plasma Level† (mg./L.)	ESR Response (mm./hr.)		Grade Response*	
						Before	After	Phenylbutazone	Cortisone
W. A.	55, M	4	2	82	...	28	16	II	I
L. C.	30, F	1½	2	56	112	30	22	II	II
H. G.	19, M	1	2	24	134	44	23	II	II
T. H.	47, M	1	2	22	100	32	16	II	not treated
G. M.	53, M	5	3	105	128	27	10	II	II
E. W.	67, F	½	3	8	102	..	..	II	not treated
V. B.	41, F	2	3	20	...	31	27	II	II
W. H.	30, M	9	3	65	86	33	23	II	not treated
L. B.	42, M	9	3	46	56	26	32	III	III
B. W.	49, F	3	3	36	108	30	34	III	III
G. S.	54, F	14	3	16	74	49	28	III	II
G. Mc.	53, M	14	3	20	100	28	15	III	III
F. B.	47, F	3	3	15	69	34	37	III	III
L. G.	30, F	9	3	20	145	38	38	III	not treated
C. C.	59, F	5	4	70	84	41	41	III	III
A. M.	56, M	33	4	12	142	38	34	III	III
M. F.	52, F	11	4	11	95	15	34	III	III
R. W.	33, F	2	2	8	101	43	38	IV	not treated

* Classification of the American Rheumatism Association.

† Patients received orally 800 mg. phenylbutazone per day, and plasma levels were measured periodically just prior to the first daily dose.

TABLE III

PLATEAU PLASMA LEVELS OF PHENYLBUTAZONE IN THREE PATIENTS ON SUCCESSIVE DOSAGE REGIMENS OF THE DRUG

Daily Dose of Drug	Subject		
	B. W.	C. C.	F. B.
mg.	mg./L.	mg./L.	mg./L.
800	107	96	55
1,200	108	108	65
1,600	118	110	69

* We are grateful to Drs. R. H. Freyburg, Hospital for Special Surgery; C. A. Ragan, Department of Medicine, College of Physicians and Surgeons, Columbia University; and O. Steinbrocker, Lenox Hill Hospital, New York, N. Y., for making available the plasma samples.

patients. It must be stressed, however, that no attempt was made to control edema either by restriction of sodium intake or by the administration of diuretics. When mercuhydrin® was required transfusion and the other recovered uneventfully when the drug was stopped.

Epigastric distress with or without nausea and vomiting was severe enough to require dis-

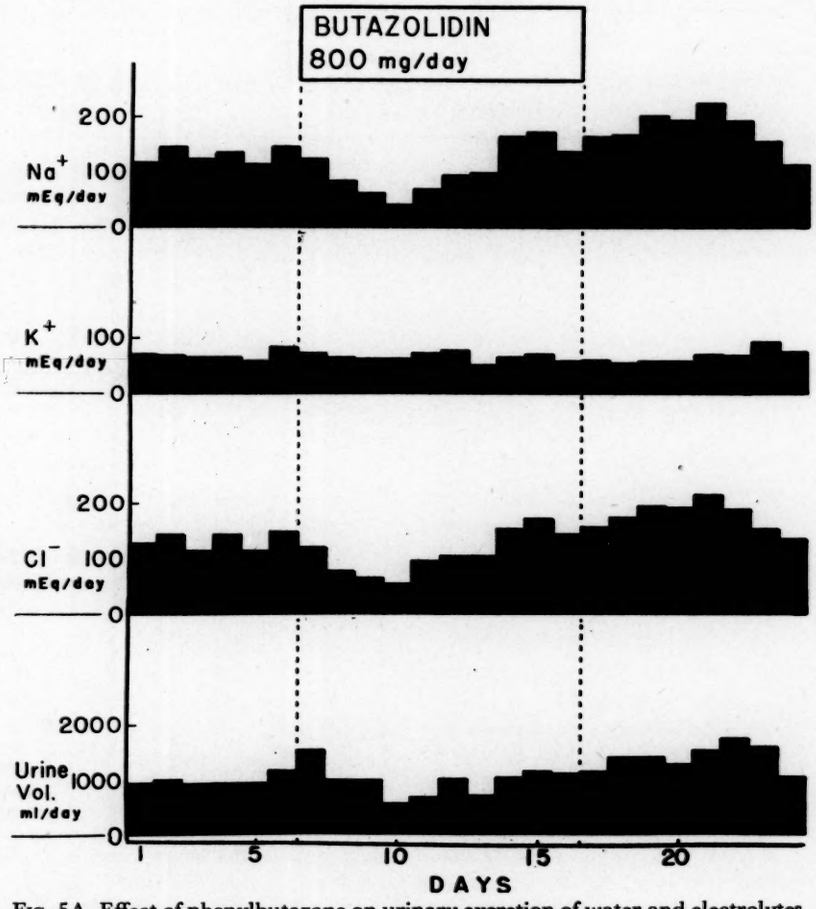

FIG. 5A. Effect of phenylbutazone on urinary excretion of water and electrolytes. Subject on regular diet (125 to 150 mEq. sodium/day).

administered to one of these patients (A. M.) a marked sodium and water diuresis and a loss of 2.5 kg. weight occurred even though the plasma levels of phenylbutazone were in excess of 100 mg. per L.

A number of patients on phenylbutazone therapy had a fall in hematocrit, red blood cell count and hemoglobin, all of which returned to pretreatment values within a few days after stopping the drug. Evidence will be presented in a subsequent section to show that the apparent anemia was not due to a reduction in red blood cell mass but to an expansion of plasma volume.

Gastrointestinal hemorrhages occurred in two patients, one of whom had evidence of pre-existing ulcer while the other had no clinical or radiographic evidence of peptic ulcer. One continuance of therapy in four patients. Skin manifestations of various types which cleared spontaneously on discontinuance of therapy were observed in six patients, including one case of urticaria. In one patient with a pre-existing superficial decubitis ulcer a severe Proteus vulgaris infection developed while on phenylbutazone. One case of stomatitis without leukopenia was observed.

In five patients elevation of blood urea nitrogen occurred which promptly returned to pretreatment levels when the drug was discontinued. In four of the five cases the drug was given a second time and elevation of the blood urea nitrogen did not recur.

Fasting blood and urinary sugar determinations were carried out at various times on

twenty-four non-diabetic patients while on phenylbutazone. No evidence was found of hyperglycemia or glycosuria in any patient during or after phenylbutazone administration.

Although some of the undesirable effects of the drug, such as development of edema and reactivation of peptic ulcers, were similar to those produced by cortisone, other effects of a

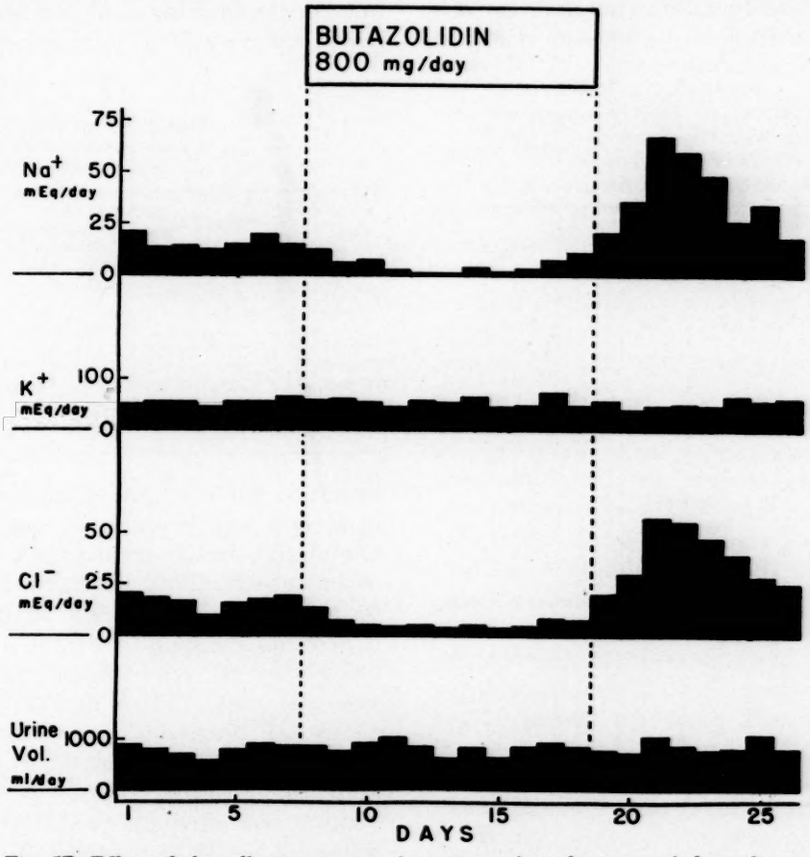

FIG. 5B. Effect of phenylbutazone on urinary excretion of water and electrolytes. Same subject on low salt diet (20 mEq. sodium/day).

Complete blood counts made weekly in almost all of the eighty-seven patients who received phenylbutazone showed no significant alteration of the white blood count or differential pattern.

In an attempt to explain the episodes of gastrointestinal bleeding the effect of the drug on blood coagulation mechanisms and capillary fragility was studied. Serial platelet counts on twenty-four patients, using both the direct chamber count and the indirect smear, did not reveal a significant variation in the number of platelets. Platelets were also measured in the patient who had gastrointestinal bleeding of unexplained origin and at no time did the platelet count fall below 200,000 per cu. mm. In sixteen subjects studied there was no significant change in bleeding time, capillary fragility, prothrombin time (whole and diluted plasma), prothrombin consumption or antithrombin activity.

hormonal nature (moon face, muscular weakness, psychoses) associated with the use of cortisone were not observed.

The occurrence of undesirable effects necessitated discontinuing the administration of phenylbutazone in 20 per cent of the eighty-seven patients treated.

PHYSIOLOGIC STUDIES

Effect of Phenylbutazone on Urinary Excretion of Water and Electrolytes. The effect of phenylbutazone on urinary excretion of water and electrolytes was studied in five normal subjects maintained on a daily sodium intake of 125 to 150 mEq. per day. The excretion of sodium, potassium and chloride was measured daily during a control period of seven days and during a period of ten days while the subjects received 800 mg. per day of the drug. In one subject (J. L., Fig. 5A) the excretion of sodium

progressively fell from about 130 mEq. per day in the control period to a minimum of 40 mEq. per day after four days on phenylbutazone, followed by a gradual return to control values during the remaining period of administration. The daily urine volume dropped from about 1,000 ml. to a minimum of 560 ml. after four days on phenylbutazone, followed again by a gradual rise to control levels. The pattern of chloride excretion was similar to that of sodium. No change in potassium excretion was observed. During this period the weight of the subject increased by 2.5 kg. After stopping medication diuresis started on the second day with a gradual loss of the retained sodium, chloride and water, and a return of body weight to the pretreatment value. Comparable results were observed in the four other normal subjects.

Plasma concentrations of sodium, potassium and chloride changed significantly in only one of the five normal subjects receiving the drug. In this subject sodium levels increased from 137 to 151 mEq./L. and chloride from 100 to 115 mEq./L., and returned to the original levels within a few days after discontinuing the drug.

The effect of phenylbutazone on urinary electrolytes was studied in two of the aforementioned subjects who were maintained on a low salt diet of about 25 mEq. per day. One subject (J. L., Fig. 5B) excreted an average of 20 mEq. of sodium daily during an eight-day control period. During the ten days of phenylbutazone administration the sodium excretion fell to an average of 5 mEq. per day. Chloride excretion fell in a parallel manner. The increase in weight which occurred was less than 1 kg. Essentially similar results were obtained in the other subject. Thus on a low sodium diet the sodium retention, though significant, is minimized and the gain in weight is small.

TABLE IV
EFFECT OF PHENYLBUTAZONE ON THE EXCRETION OF URINARY SODIUM AND POTASSIUM IN PATIENTS WITH RHEUMATOID ARTHRITIS
(Dose: 800 mg./day orally)

Day of Dose	T. H.		B. W.		L. C.		L. B.	
	Na	K	Na	K	Na	K	Na	K
	(mEq./day)		(mEq./day)		(mEq./day)		(mEq./day)	
−2	73	53	64	30	9	45	40	67
−1	82	61	33	26	11	33	56	48
0	77	59	54	40	12	34	86	59
1*	33	53	30	20	1	11	55	44
2	11	52	4	14	1	21	7	29
3	35	51	18	16	1	26	2	25
4	23	37	41	43	1	30	5	58
5	16	25	58	28	1	23	12	37
6	28	26	20	25	2	49		
7	55	31	47	30	1	13	82	66
8	46	41	60	16	3	34	92	67

* Administration of phenylbutazone began on this day.

TABLE V
BLOOD VOLUME CHANGES IN A PATIENT (E. P.) RECEIVING PHENYLBUTAZONE
(Dose: 800 mg./day orally for forty-six days)

Time After Dose	Hematocrit	Total Blood Vol. (ml.)	Plasma Vol. (ml.)	Red Cell Mass (ml.)	RBC	
					Hgb. (gm. %)	(millions/mm.³)
Control....	50	3,360	1,762	1,598	14.8	5.4
14 days.....	45	3,500	2,000	1,500	14.5	4.8
23 days.....	39	4,290	2,700	1,590	13.5	4.7
46 days.....	40	4,280	2,650	1,630	13.5	4.0

Urinary excretion of sodium and potassium was also measured in five of the arthritic patients on phenylbutazone therapy. Although the control of sodium intake in these ill patients was not possible, the drop in excretion of sodium was obvious. (Table IV.) The patients gained 2.5 to 4 kg. in weight during the eight-day period of phenylbutazone, with a diuresis and loss of weight on discontinuing therapy.

Effects of Urinary 17-Ketosteroids. The urinary excretion of 17-ketosteroids was assayed at various times in six arthritic patients, before, during and after phenylbutazone administration. No increase was observed on administration of phenylbutazone.

Effect on Eosinophils. Phenylbutazone did not cause significant eosinopenia in seven arthritic and five non-arthritic patients after repeated oral doses of 800 mg. daily for periods up to two weeks.

Effect on Blood Volume. The effect of phenylbutazone on blood volume was studied in five non-arthritic patients given 800 mg. phenylbutazone per day. Detailed data for one patient (E. P., Table V) clearly show that during drug therapy there was a fall in hematocrit, red cell count and hemoglobin, and an increase in total blood volume. However, the red cell mass remained essentially constant and the afore-

mentioned changes could be attributed to an expansion in plasma volume. In the five patients studied, increases in plasma volume up to 50 per cent were noted during the period of study. (Table VI.) The reversibility of the phenomenon is seen in patient F. M., whose plasma volume after six days of therapy increased from 1,370 to 1,840 ml. After an interval of five days without drug the plasma volume returned to near pretreatment levels. Throughout the period of phenylbutazone therapy these subjects showed no change in reticulocyte count, serum bilirubin or red cell fragility.

TABLE VI
BLOOD VOLUME CHANGES IN PATIENTS RECEIVING PHENYLBUTAZONE

Patient	Oral Dose	Maximum Hematocrit Change	Maximum Change In Plasma Vol. (ml.)	Maximum Change in Red Cell Mass (ml.)
M. F.	800 mg./day × 10	45–40	1990–2470	1480–1520
G. K.	800 mg./day × 112	42–38	2285–2950	1505–1540
P. C.	800 mg./day × 10	42–38	2590–3070	1720–1730
F. M.	800 mg./day × 6	48–42	1370–1840*	1135–1220
F. M.	Drug discontinued for 5 days	42–45	1840–1430†	1220–1060

* Presence of congestive heart failure.
† Signs of congestive heart failure disappeared.

DISCUSSION

The present study indicates that phenylbutazone exerts antirheumatic effects in rheumatoid arthritis which compare favorably with those produced by cortisone. The antirheumatic effects of phenylbutazone, together with its effects on electrolyte and water excretion and its propensity to reactivate ulcers, raise the question whether the drug exerts its action through the adrenal-pituitary axis. However, phenylbutazone does not appear to cause potassium diuresis, eosinopenia or increased ketosteroid excretion. Clinical signs of hyperadrenalism and psychosis have not been observed. From these observations it seems unlikely that the actions of phenylbutazone are mediated either directly or indirectly through stimulation of the adrenal cortex. Kuzell et al.[2] reached similar conclusions on the basis of the failure of the drug to affect the adrenal ascorbic acid content of rats.[2]

There is considerable variability in the therapeutic response to phenylbutazone among different patients. One of the reasons for this may lie in the considerable individual differences in rate of metabolic transformation of the drug. However, this cannot be the only factor since clinical results indicate that even when different patients are maintained at similar plasma levels of the drug there are still wide discrepancies in the therapeutic response.

Phenylbutazone in rheumatic patients, as in normal individuals, behaves in an unusual manner in that plasma levels of the drug approach a limiting concentration as the dosage is increased. Since subjects on a dosage schedule of 1,600 mg. daily achieve plateau plasma levels of phenylbutazone which are not appreciably higher than those achieved on a dosage schedule of 800 mg. there is no advantage to be gained in administering more than 800 mg. of the drug daily. If the desired therapeutic effect is not achieved on this dosage regimen, further benefit should not be expected with increase in the dose. In fact most subjects achieve plasma levels on a daily dosage of 400 to 600 mg. daily that are only slightly lower than those achieved when 800 mg. are given. These observations agree with those made clinically by Stephens et al.[16] who observed that only rarely did increased therapeutic effect result from increasing the daily dosage above 600 mg.

Phenylbutazone exerts a variety of side effects of which the more serious include edema, gastrointestinal hemorrhage and agranulocytosis. An effect on salt and water metabolism has also been observed by other investigators.[17,18] This property of phenylbutazone necessitates caution in the administration of the drug in the presence of cardiac, renal or hepatic disease. Present indications are that sodium and water retention can be diminished by restriction of sodium intake during the administration of the drug. The presence of pre-existing peptic ulcers should be a contraindication to the use of the drug. Leukopenia and agranulocytosis have not been observed in this study although these complications have been reported elsewhere.[3,19,20] The fall in red blood cell count and hemoglobin reported by others[3,16] has been regularly observed in these studies but has been shown to be due primarily to an increase in plasma volume

without increased destruction or decreased formation of red cells. The red cell count and hemoglobin return promptly to previous levels upon discontinuance of the drug. The effect of phenylbutazone in increasing the plasma volume is similar to that which has been reported to accompany fluid retention on corticotropin and cortisone therapy.[21–23]

It would appear, therefore, that phenylbutazone, a relatively simple synthetic compound, can produce antirheumatic effects comparable to those elicited by cortisone and corticotropin. The encouraging clinical results obtained should serve to direct further investigation toward other non-steroidal compounds which may exert desirable local tissue effects without the hormonal imbalances that may accompany the administration of cortisone and corticotropin.

SUMMARY

1. Phenylbutazone exhibits antirheumatic effects in rheumatoid arthritis which are comparable to those shown by cortisone and corticotropin.

2. Like cortisone and corticotropin the drug causes urinary retention of sodium, chloride and water, and may reactivate peptic ulcers; but unlike cortisone it does not affect the excretion of potassium nor does it cause eosinopenia or increased ketosteroid excretion. It is concluded that the action of phenylbutazone is not mediated, directly or indirectly, through the adrenal cortex.

3. During phenylbutazone therapy there is often a fall in red cell count, hemoglobin and hematocrit which is primarily the result of hemodilution and not of depression of the hematopoietic system.

4. Plasma levels of phenylbutazone approach a limiting concentration as dosage is increased. This limiting concentration varies widely from patient to patient. Most subjects achieve plasma levels on 400 to 600 mg. daily that are only slightly lower than when 800 mg. are given.

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The Sensitized Sheep Cell Agglutination Reaction in Rheumatoid Arthritis*

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THE enhancing effect of sera from patients suffering from rheumatoid arthritis on the agglutination of sheep red cells by rabbit anti-sheep cell serum was described by Waaler[1] in 1940. In 1948 Rose and others[2] made similar observations and devised a serologic test based on this phenomenon. This test involved titration of the patient's serum with sheep red cells and also with sheep red cells to which a small and predetermined "sensitizing" dose of rabbit anti-sheep cell serum had been added. When the agglutinating titer for sensitized cells was 16 or more times greater than the titer for unsensitized cells, the serum was almost exclusively found to be derived from a case of rheumatoid arthritis.

The test has now been studied by several investigators[1–13] whose results are summarized in Table 1. A modification of the Rose technic, introduced by Heller et al.[5], Svartz and Schlossmann[10] and Ball,[8] entails the removal from the patient's serum of the naturally occurring heterophil antibodies by absorption with sheep red cells. This procedure has been shown to have no effect on the subsequent titer of the serum for sensitized cells. In a comparative experiment Heller and others[5] found the modified test to be more sensitive but no less specific than the Rose test.

TABLE 1
RESULTS OBTAINED IN THE SENSITIZED SHEEP CELL TEST BY OTHER WORKERS

Authors	No. of Sera from Cases of Rheumatoid Arthritis	Positive (%)	No. of Other Sera Tested	Positive (%)
Waaler (1940)	77	33	202	4
Rose et al. (1948)	43	37	67	4
Brown et al. (1949)	62 (active)	55	83	1
	20 (inactive)	30		
Jawetz and Hook (1949)	20 (active)	65	82	2
	37 (moderately active)	14		
	21 (inactive)			
*Heller et al. (1949)	39 (active)	90	111	2
	7 (doubtful activity)	14		
	8 (inactive)			
Miller et al. (1949)	21	68	23	35
Sulkin et al. (1949)	35	45	113	1
*Ball (1950)	286	49	609	2
Dordick and Wasserman (1950)	21 (active)	61	181	12
*Svartz and Schlossmann (1950)	180	90	283	4
Wager (1950)	92	61	1049	2
Scott (1952)	124	60.5	172	8
*Ball (1952)	642	44.2	1301	2.5

* Titers determined after absorption of sera with unsensitized sheep red cells.

This report is based on work undertaken to investigate the usefulness of the sensitized sheep

* From the Section of Preventive Medicine and the Department of Internal Medicine, Yale University School of Medicine, and The Arthritis Clinic of the Grace-New Haven Community Hospital, New Haven, Conn. The expenses of this investigation have been defrayed by a grant from the U. S. Public Health Service.

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cell test as an aid in the diagnosis of rheumatoid arthritis and assessement of disease activity. The results of the test performed on 350 individual sera are presented in Table II. In addition, the results of serial studies in seven cases of rheumatoid arthritis are discussed.

TABLE II
RESULTS OF THE SENSITIZED SHEEP CELL TEST IN RHEUMATOID ARTHRITIS AND OTHER CONDITIONS

Diagnosis	No. of Sera (Individual Patients)	No. of Positive Tests	Percentage of Positive Tests
Rheumatoid arthritis	51 (5)	38 (5)	75
Rheumatoid arthritis (diagnosis uncertain)	29	7	24
Ankylosing spondylitis	11	...	....
Still's disease	7	...	....
Arthritis with psoriasis	5	...	....
		...	....
Total	23	...	....
Osteoarthritis	20	...	....
? Gout	6	...	....
Lupus erythematosus	6	...	....
Scleroderma	3	1	....
Periateritis nodosa	2	...	....
? Dermatomyositis	1	...	....
Osteochondritis dissecans	1	...	....
Hydrarthrosis	2	...	....
Non-articular rheumatism	5	...	....
Rheumatic fever (acute)	14	...	....
Rheumatic fever (inactive)	17	...	....
Chorea	2	...	....
Total	79	1	1.3
Non-rheumatic diseases	71	...	....
Serology laboratory sera (unknown diagnosis)	50	...	....
Normal individuals	42	...	....
Total sera examined	350	...	....

CLINICAL MATERIAL

The majority of sera from other than healthy individuals was obtained from the wards and clinics of the Grace-New Haven Community Hospital.* Sera were stored at −10°C. and in a few instances had been preserved for periods up to two years. All sera were inactivated at 56°C. for thirty minutes prior to use.

Rheumatoid Arthritis. This group comprised fifty-one patients with polyarthritis, typical clinically and radiographically of rheumatoid arthritis. Ages ranged from twenty-one to seventy-three years and disease duration from ten months to twenty-seven years. Females outnumbered males in the ratio 2:1.

Five cases of clinically typically rheumatoid arthritis in which radiographs were not available have been excluded from the group but the results of the sensitized sheep cell test have been indicated parenthetically in Table II.

Rheumatoid Arthritis (Diagnosis Uncertain). Twenty-nine patients in whome the diagnosis of rheumatoid arthritis could not be confirmed because of insufficient clinical data or equivocal clinical features have been included.

Diseases Closely Related to Rheumatoid Arthritis. Ankylosing spondylitis: Radiographic changes were present in nine patients. In the remaining two patients radiographs were not available, but the clinical appearances were typical.

Still's disease: Sera from seven patients were studied. The age of onset of polyarthritis ranged from two to fifteen years. Radiographic changes were present in four patients. In one of the remaining patients the subsequent clinical course confirmed the original diagnosis. No detailed clinical accounts were available on the other two patients.

Arthritis with psoriasis: In four of the five patients the arthritic changes were radiographically typical of rheumatoid arthritis. The remaining patient showed intermittent joint swelling without radiographic changes.

Other Diseases with Arthritic Manifestations. Of the forty-six patients in this group twenty had clinical symptoms and radiographic changes diagnostic of osteoarthritis. In none of the six patients with "gout" was the evidence for this diagnosis unequivocal. Sera were obtained from fourteen patients with acute rheumatic fever during the active phase of the disease. Sera from two patients with Sydenham's chorea were tested. Seventeen patients had evidence of subacute or chronic rheumatism but without present symptoms of acute rheumatic fever.

Non-rheumatic Diseases Group. Seventy-one sera from patients suffering from diseases without articular manifestations were tested. Twenty of these sera were obtained from patients with diseases of known or probable streptococcal etiology.

Serology Laboratory Sera. No clinical data were available on these sera. They were collected from pregnant women and from patients attending the hospital with a variety of diseases.

Normal Individuals. Thirty-eight of the forty-two sera* were obtained from presumably healthy young adults at an Army Induction Center. The remaining four sera were from healthy staff members.

* Some sera were supplied through the kindness of Dr. George Friou, Veterans Administration Hospital, Newington, Conn.

* Kindly supplied by Dr. Leon A. Phillips.

REAGENTS AND METHODS

Sheep Red Cells. The sheep red cells used in the test were obtained commercially. Those found most satisfactory were supplied as a 50 per cent suspension of pooled sheeps' blood in citrate. The cells were stored at 4°C. on arrival (within forty-eight hours of bleeding) and were not used for at least twenty-four hours. Fresh supplies were received weekly.

Cells were washed three times in 0.89 per cent saline in each phase of the test.

Rabbit Anti-sheep Cell Serum (Hemolysin). Glycerinated hemolysin was obtained commercially. Stock dilutions were prepared as required and stored at −10°C. The dilution figures given for hemolysin refer to the glycerinated preparation which contained aliquots of hemolysin and glycerin.

Diluent. Eighty-nine hundredths per cent saline was used throughout.

Controls. At least two sera of known titer were included in each batch of sera tested.

Technic of the Test. The method used was based on that of Heller and others[5] and involved three main procedures: (1) Absorption of heterophil agglutinins from the human serum by means of sheep red cells; (2) determination of the sensitizing dose of hemolysin; (3) titration of the absorbed serum with sensitized sheep red cells.

1. Absorption of Heterophil Agglutinins from Human Serum. To 0.4 ml. undiluted serum (inactivated at 56°C. for thirty minutes) was added 0.4 ml. of 25 per cent sheep cell suspension in saline.* This remained at room temperature for forty minutes with thorough shaking at ten-minute intervals. The suspension was centrifuged at 2,000 r.p.m. for fifteen minutes and 0.5 ml. of supernate was transferred to a tube containing 0.5 ml. of 25 per cent sheep cells. The absorption was repeated at room temperature for a further forty minutes and the tube kept at 4°C. overnight. The suspension was again centrifuged and the absorbed serum removed for use in the final titration. As a result of the absorption procedure the original serum was now diluted 1 in 4.

2. Determination of the Sensitizing Dose of Hemolysin. In the original Rose test the sensitizing dose of hemolysin was determined on the basis of the hemolytic titer, 2 minimal hemolytic doses being used to sensitize the sheep red cells. However, Pike and others[14] found that the ratio of the hemolytic to agglutinating titer of hemolysin was not constant and, as indicated by Heller and others,[5] it would therefore seem preferable to standardize the dose of hemolysin on its agglutinating rather than hemolytic properties.

In the early stages of the present work the sensitizing dose of hemolysin was determined by direct titration with sheep red cells. From this procedure the minimum concentration of hemolysin capable of producing agglutination of a given batch of cells was determined and a fraction (1/5) of this used to sensitize the cells in the final titration. Provided that this fraction was kept constant in each batch of tests, consistent results were obtained. Later the preliminary direct titration of cells and hemolysin was abandoned, the sensitizing dose being determined by titrating cells treated with varying hemolysin concentrations with a "standard" serum of known and high titer.

Direct titration of cells and hemolysin: Dilutions of stock hemolysin in concentrations of 1:300, 1:400, 1:500, 1:600 . . . 1:1200 were prepared. To 0.3 ml. of each dilution were added 0.3 ml. of 1 per cent sheep cell suspension. The tubes were placed in a waterbath a 37°C. for one hour and thereafter refrigerated at 4°C. overnight. Agglutination titers were read immediately after removal from the refrigerator. The tubes were tapped firmly until there was no cell deposit at the bottom. Three grades of agglutination were recorded: (1) fine granulation visible to the naked eye, (2) coarser granulation with pink supernate, (3) firm disc or large clumps: clear, or faint pink supernate.

The agglutination titer was taken as the dilution in the last tube in which fine granulation was seen. One-fifth of the agglutinating concentration was used for sensitization of the cells in procedure (3). For example, if the highest dilution showing agglutination was 1:1000, the cells were sensitized with hemolysin in a concentration of 1:5000.

Indirect titration of hemolysin using "standard" serum: A serum of high titer (as determined in a previous test) was used as a control. Heterophil agglutinins were removed from the serum by the method just described. Sufficient serum was absorbed for use over a period of one to two months and stored at −10°C. The absorbed serum was diluted in saline to a concentration equal to the previously known agglutinating titer. A 1 per cent suspension of sheep cells was sensitized with aliquots of hemolysin in concen-

* Cell concentrations are expressed as percentage volumes of packed cells.

trations of 1:3000, 1:4000, 1:5000, 1:6000, 1:7000. The cell-hemolysin suspensions were transferred to a waterbath at 37°C. for fifteen minutes. To 0.3 ml. in each tube was added 0.3 ml. of the diluted "standard" serum. The tubes were returned to the waterbath at 37°C. for one hour and refrigerated at 4°C. overnight. Readings were made as in the first method. The tube containing the lowest concentration of hemolysin in which agglutination occurred with the "standard" serum was taken as the end-point and this hemolysin concentration was used for subsequent sensitization of the cells in procedure (3).

3. Titration of Absorbed Serum with Sensitized Cells. Serial dilutions in saline ranging from 1:4 to 1:1024* were prepared from the absorbed serum in procedure (1), each tube containing 0.3 ml. To the first tube 0.3 ml. of 0.5 per cent sheep cell suspension was added.

Sensitized sheep cells were prepared by mixing aliquots of 1 per cent sheep cells and hemolysin in concentration as previously determined in procedure (2). The cell-hemolysin suspension was transferred to a waterbath at 37°C. for fifteen minutes; 0.3 ml. of this suspension was added to each dilution of serum from 1:8 to 1:1024. All tubes were placed in a waterbath at 37°C. for one hour and then refrigerated at 4°C. overnight. Agglutination titers were read immediately after removal from the refrigerator and the criteria of agglutination were identical with those used in procedure (2).

The "standard" serum used for determining the sensitizing dose of hemolysin was included in each test. A further control serum of low titer was also included.

No result was considered valid if there was agglutination in the first tube (which contained absorbed serum and unsensitized cells). The presence of agglutination in this tube indicated that absorption of heterophil agglutinins was incomplete.

RESULTS AND COMMENTS

In the "rheumatoid arthritis" group 75 per cent of fifty-one individual sera were positive, a titer of 1:64 and higher constituting a positive test. (Table II.) This line of demarcation was chosen (after examining the results of 350 individual tests) as offering the greatest specificity without serious reduction in sensitivity. The choice of a lower titer would have resulted in greater sensitivity but only at the expense of specificity. For example, 88 per cent of the fifty-one sera showed titers of 1:16 and higher, but so also did 20 per cent of twenty sera from patients suffering from osteoarthritis.

Correlation of disease activity and titer levels was not attempted, as in several instances clinical details were insufficient for accurate definition of activity. Of the thirteen negative sera eight were obtained from patients who had had the disease for eleven years or more. In six cases the disease was active as judged by the presence of joint pain and swelling and increase of the erythrocyte sedimentation rate. All but one of the thirteen negative sera were derived from female patients, the ratio of females to males in the group being 2:1. The finding of a higher proportion of negative tests in females conforms with the findings of Ball.[13]

Analysis of the results obtained in the "rheumatoid arthritis, diagnosis uncertain" group is difficult. Of the seven sera giving positive tests the clinical evidence strongly favored a diagnosis of rheumatoid arthritis in four patients, in all of whom symptoms had been present for eighteen months or more. However, six of the twenty-two patients with a negative test had had polyarthritis of from six to twelve months' duration and might well have been early cases of rheumatoid arthritis. Clearly, the exclusion of this group from the series would give an unduly optimistic impression of the sensitivity of the test.

The negative results obtained in Still's disease (juvenile rheumatoid arthritis) and ankylosing spondylitis are noteworthy. The number of cases in these groups is small but Scott[12] found that only 13.5 per cent of thirty-seven cases of Still's disease were positive as compared with 60.5 per cent of 124 cases of rheumatoid arthritis. Rose and others,[2] Jawetz and Hook,[4] Heller et al.[5] and Ball[8,13] found only a very few positive tests in cases of ankylosing spondylitis.

Of all other sera examined only one showed a titer higher than 1:64. This was obtained from a typical case of scleroderma of two years' duration.

SERIAL STUDIES

In seven of the fifty-one cases of rheumatoid arthritis serum was collected at intervals over periods ranging from six to sixteen months. Sera from each patient were stored at −10°C. and titrated in one batch.

The activity of the disease was estimated by

* These dilution figures refer to the concentration of the original unabsorbed serum.

the presence of joint tenderness and swelling and elevation of the erythrocyte sedimentation rate. In this report no attempt has been made to record finer degrees of activity and only three grades are shown in the accompanying figures, ranging from remission (0) to acute relapse with

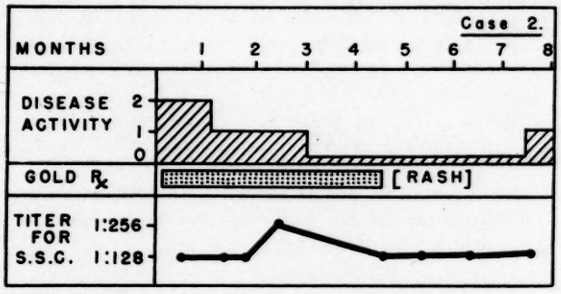

FIG. 1. Clinical record and sensitized sheep cell titers (S.S.C.) in a patient treated with gold.

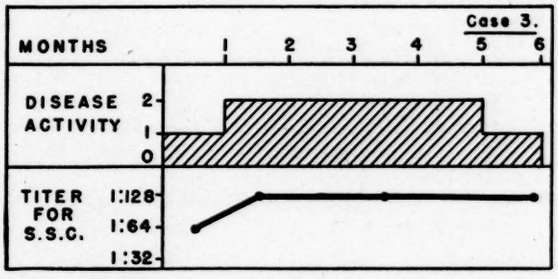

FIG. 2. Clinical record and S.S.C. titers in an untreated patient.

joint swelling and tenderness accompanied by elevation of the erythrocyte sedimentation rate (2).

In Cases 1 and 5 the agglutination titers were below 1:64, constituting a negative test. In the remaining cases the test was positive but only in Case 6 (Fig. 3) was there a change in titer of more than one tube. Such minor variations lie within the experimental error of the test.

In Case 6 there was a marked change in activity of the disease, the patient having a good response to cortisone therapy on two occasions, accompanied by a steady reduction of the erythrocyte sedimentation rate during and after the second course of cortisone. The sensitized sheep cell titer did not alter significantly. Similarly in Case 2 (Fig. 1) when remission occurred there was no change in the sensitized sheep cell titer. In Case 3 (Fig. 2) there was progressive clinical deterioration unreflected by the sensitized sheep cell titer. In the remaining cases the activity of the disease changed little throughout the study, thus paralleling the sensitized sheep cell titer. In one further patient with rheumatoid arthritis, not recorded because of insufficient clinical data, the sensitized sheep cell titer remained constant following administration of clinically effective doses of cortisone over a period of three months.

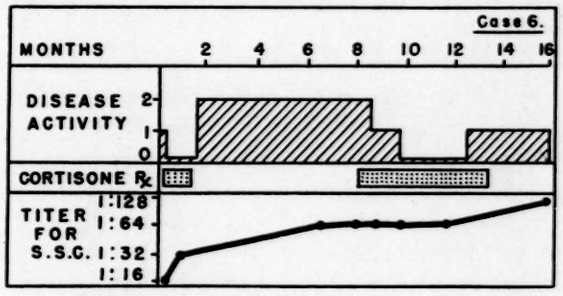

FIG. 3. Clinical record and S.S.C. titers in a patient treated with cortisone.

CONCLUSIONS

The results obtained in the examination of individual sera show that the sensitized sheep cell test is highly specific for rheumatoid arthritis and may therefore be of help in the differential diagnosis of this disease. The sensitivity of the test is, however, almost certainly less than the figure of 75 per cent positive sera in the rheumatoid arthritis group would indicate; this group contains cases only in whom the diagnosis was beyond doubt. The inclusion of the "rheumatoid arthritis, diagnosis uncertain" group considerably reduces the sensitivity of the test. It is believed with Ball[13] that the differing figures reported by various investigators may in part be due to lack of uniformity in the choice of diagnostic criteria.

In the present series a positive test was not obtained in any case of rheumatoid arthritis of less than eighteen months' duration, a discouraging finding in relation to the usefulness of the test as an aid to early diagnosis. However, only a few sera from early cases were available and other investigators, notably Ball,[13] have obtained more encouraging results.

The serial studies indicate that the sensitized sheep cell titers do not reflect changes in disease activity, whether such changes occur naturally or as the presumed result of gold or cortisone therapy.

SUMMARY

1. A method of performing the sensitized sheep cell test using commercial reagents is described.

2. Seventy-five per cent of fifty-one sera from known cases of rheumatoid arthritis and 24

per cent of twenty-nine sera from unconfirmed cases of rheumatoid arthritis were positive.

3. Only 1 of 102 sera from patients with other diseases with articular manifestations was positive. Sera from 121 patients with non-articular diseases and from forty-two healthy individuals gave negative results.

4. Serial studies on seven patients showed that the serum titer for sensitized sheep cells did not reflect changes in disease activity.

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The Systemic Lesions of Malignant Rheumatoid Arthritis*

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THE incidence of rheumatic heart disease found in postmortem examination of patients with rheumatoid arthritis is said to be significantly higher than in the general hospital population.[1–3,12] There is, however, clinical evidence that valvulitis and other stigmata of rheumatic heart disease are infrequent in patients with rheumatoid arthritis except when a straightforward history of rheumatic fever can be obtained.[3,4]

It is our purpose to report the cases of two patients with active rheumatoid arthritis whose fulminating clinical course was characterized by pleurisy and pericarditis. At autopsy widespread visceral lesions differing from those seen in patients dying with rheumatic fever were found.

CASE REPORTS

CASE I. (Figs. 1 and 2.) C. H., a fifty-two year old switchboard operator, was admitted to the Columbia Research Division of the Goldwater Memorial Hospital for the management of rheumatoid arthritis which had relapsed after cessation of cortisone therapy.

In 1941, at the age of forty-one, the patient developed painful swelling and redness of the small joints of her hands, ankles and shoulders, diagnosed as rheumatoid arthritis. Between 1941 and 1946 her disease continued active despite frequent hospitalizations, with full therapeutic regimens including salicylates, chrysotherapy and multiple vaccines. In 1946 she was admitted to the Goldwater Memorial Hospital where sanitarium-like care, salicylates and chrysotherapy coincided with a clinical and laboratory remission which continued for one year. Her disease slowly relapsed, requiring readmission to the Goldwater Memorial Hospital in October, 1949. At this time she was bedridden with generalized severe arthritis. Blood pressure was 110/75. The heart was not enlarged. There was a grade II apical systolic murmur. Typical advanced rheumatoid deformities of the hands, elbows and feet were present. There was no evidence of acute inflammation of the involved joints. On admission, laboratory data included erythrocyte sedimentation rate of 93 mm. in one hour (Westergren), positive agglutination against group A hemolytic streptococci, a 2+ cephalin flocculation test, x-ray evidence of severe rheumatoid arthritis and a diabetic glucose tolerance curve. After preliminary evaluation she received corticotropin with prompt clinical improvement and a return of the erythrocyte sedimentation rate to normal. The patient became ambulatory. After two weeks corticotropin was discontinued; there was an immediate severe relapse. In March, 1950, cortisone was instituted in doses averaging 400 mg./week, resulting again in a clinical remission and resumption of ambulation. Three months after the beginning of cortisone therapy she developed a compression fracture of the fourth lumbar vertebra attributed to osteoporosis. She was given a back brace and remained up and about. Occasional glycosuria, not requiring insulin, developed during this period. She was discharged three months after the start of cortisone therapy and was followed in the Out-

* From the Research Service, First (Columbia University) Division, Goldwater Memorial Hospital, the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital, and the Departments of Medicine and Pathology, Columbia University College of Physicians and Surgeons, New York. This study was aided in part by grants from the Masonic Foundation for Medical Research and Human Welfare, and the Public Health Research Institute of the City of New York, Inc. The cortisone used in this study was supplied in part by Merck & Company, Rahway, N.J., and in part purchased with funds supplied by the U. S. Public Health Service.

† Fellow of the Arthritis and Rheumatism Foundation.

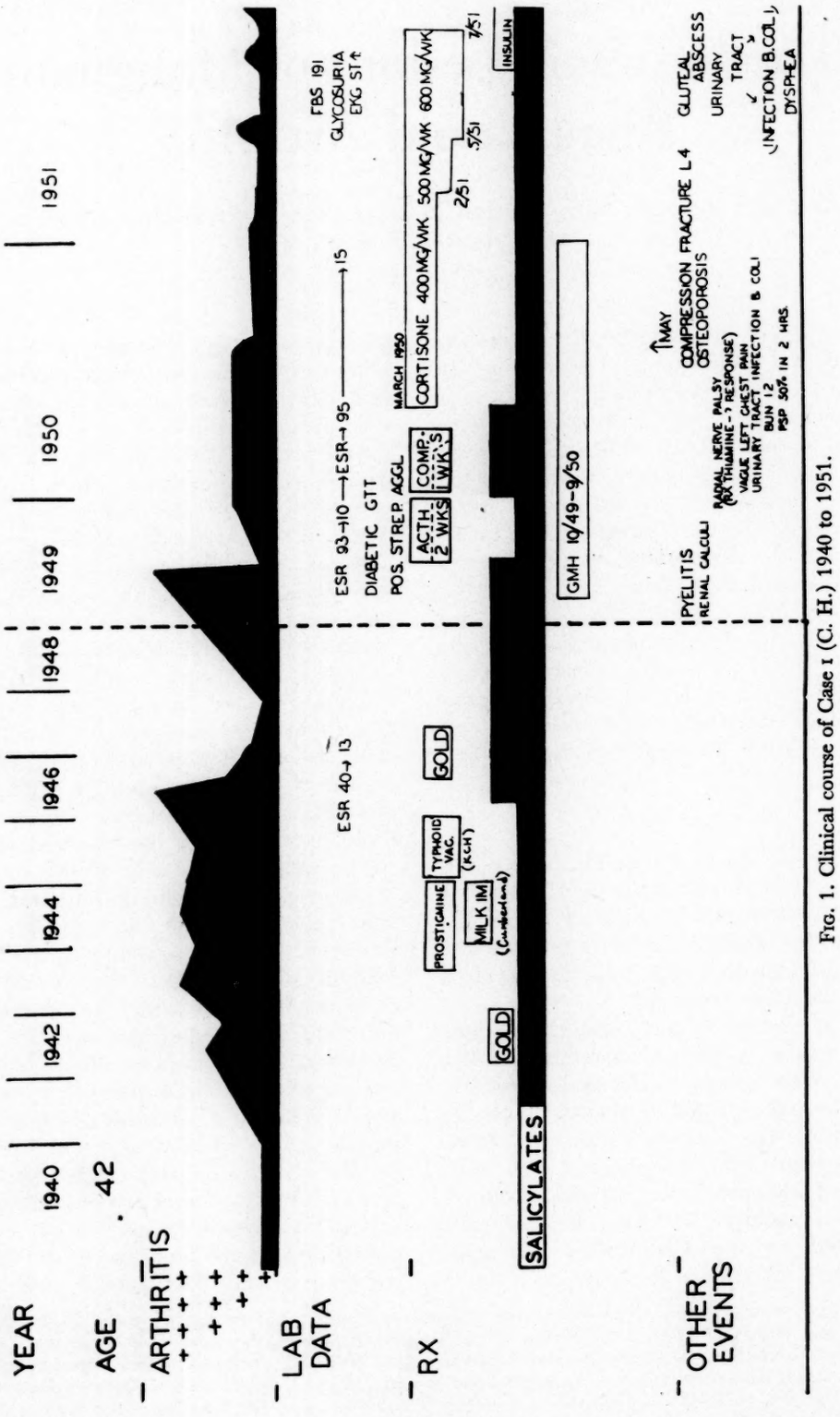

FIG. 1. Clinical course of Case 1 (C. H.) 1940 to 1951.

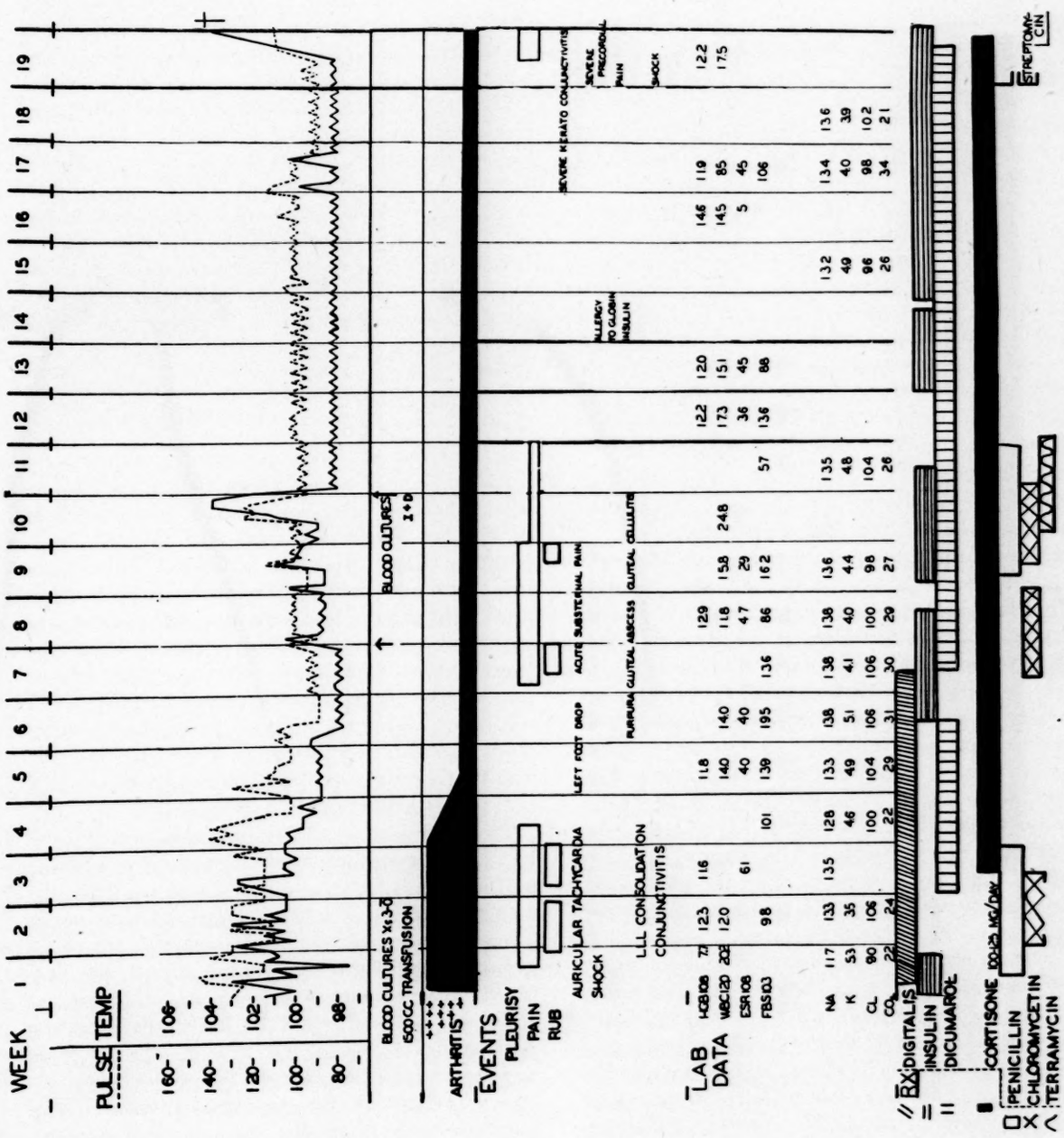

FIG. 2. Detailed course of Case 1 (C. H.) twenty weeks prior to death.

patient Department of the Presbyterian Hospital, She developed bilateral lower extremity paresthesias, thought to be due to diabetic neuropathy, and received thiamine chloride without relief.

In July, 1951, a post-injection gluteal abscess developed. She was admitted to the Presbyterian Hospital. At this time she was receiving 600 mg. of cortisone per week. Physical examination revealed generalized rheumatoid arthritis, a gluteal abscess and evidence of peripheral neuropathy involving the lower extremities. Significant laboratory data included the presence of glycosuria with a fasting blood sugar of 191 mg. per cent, serum albumin 3.0 gm. per cent and serum globulin 2.1 gm. per cent. Pyuria was present and the urine culture showed E. coli. The electrocardiogram showed elevated S-T segments in leads II, III and V_5 with no other significant changes. The cortisone was discontinued and the patient given 20 units of protamine zinc insulin daily. The gluteal abscess was incised and drained and subsequently healed. Because of severe exacerbation of her arthritis she was transferred to Goldwater Memorial Hospital on July 26, 1951, two weeks after cortisone had been discontinued.

On admission, the pertinent findings included temperature 102.4°F., pulse 132 and regular, respiratory rate 22, blood pressure 140/90. Moon facies and buffalo-type obesity were present. There was moderate conjunctival injection with episcleritis. Three small subcutaneous nodules were present over the occiput. The heart was not enlarged; the sounds were of fair quality. There were no rubs or murmurs. The lungs were clear. There was a granulating wound of the right buttock. Evidence of active arthritis in multiple joints was present. Dorsalis pedis pulses were of good quality; the ankle jerks were absent; vibratory and position senses were impaired in the lower extremities.

Laboratory data included: urine 1+ sugar, 0 albumin, 10 to 12 white blood cells, and yeasts on culture. Hemoglobin was 10.8 gm. per cent, white blood count 12,000 with 84 polymorphonuclear leukocytes, erythrocyte sedimentation rate 108 mm. in one hour. Fasting blood sugar was 103 mg. per cent. The electrocardiogram showed a regular sinus tachycardia of 130; there was a Q-S deflection in lead III; S-T segments were elevated in leads II, III and AVF and T waves were inverted or flat in all leads.

During the first two days of hospitalization her temperature ranged up to 103°F. and she was acutely ill. Three blood cultures were sterile and adequate amounts of penicillin and chloromycetin had no appreciable effect on the course of her fever. Joint pains were difficult to control with salicylates. Two days after admission an auricular tachycardia at a rate of 140 appeared, with evidence of left ventricular failure. She was digitalized but later the same day the patient went into shock with an unobtainable blood pressure. Clinical signs of shock lasted about two hours and disappeared spontaneously. Her blood pressure returned to 100/70.

The serum sodium was found to be 117 mEq./L., potassium 5.3 mEq./L., chlorides 90 mEq./L., CO_2 22 mEq./L. Her hemoglobin fell to a low of 7.7 gm. per cent with no evidence of hemorrhage or hemolysis. During the next few days she received infusions of hypertonic saline solution, glucose and 1,500 cc. of blood. She showed some temporary improvement but her fever continued as before. Four days after admission she developed pleuritic pain and a pleural rub over the left chest posteriorly. There were physical signs of consolidation over the left lower lobe. Chest x-ray showed a small amount of fluid in the left chest. Opinion was divided as to whether these findings indicated pulmonary infarction or a flare-up of systemic disease associated with rheumatoid arthritis. The patient was started on an anticoagulant regimen. Cortisone therapy was reinstituted two days after admission. She was maintained on cortisone (100 to 125 mg./day) up to the day of death. The pleural pain and rub continued intermittently for the first four weeks of hospitalization, then subsided and her arthritis began to improve.

By the fifth week of hospitalization the patient had improved sufficiently to attempt gradual ambulation. Anticoagulant therapy was discontinued after five weeks. Insulin was again started and was necessary except for brief periods throughout the remainder of her hospitalization because of uncontrolled diabetes.

In the seventh week of hospitalization the patient developed a left gluteal abscess from which a penicillin-resistant Staphylococcus aureus was cultured. She was treated with chloromycetin and later the abscess was incised, drained and subsequently healed. The same week the patient was awakened from sleep by severe substernal and precordial non-radiating pain. She was not dyspneic, blood pressure was 180/100 and pulse 76. The electrocardiogram showed diffuse non-specific change and, although

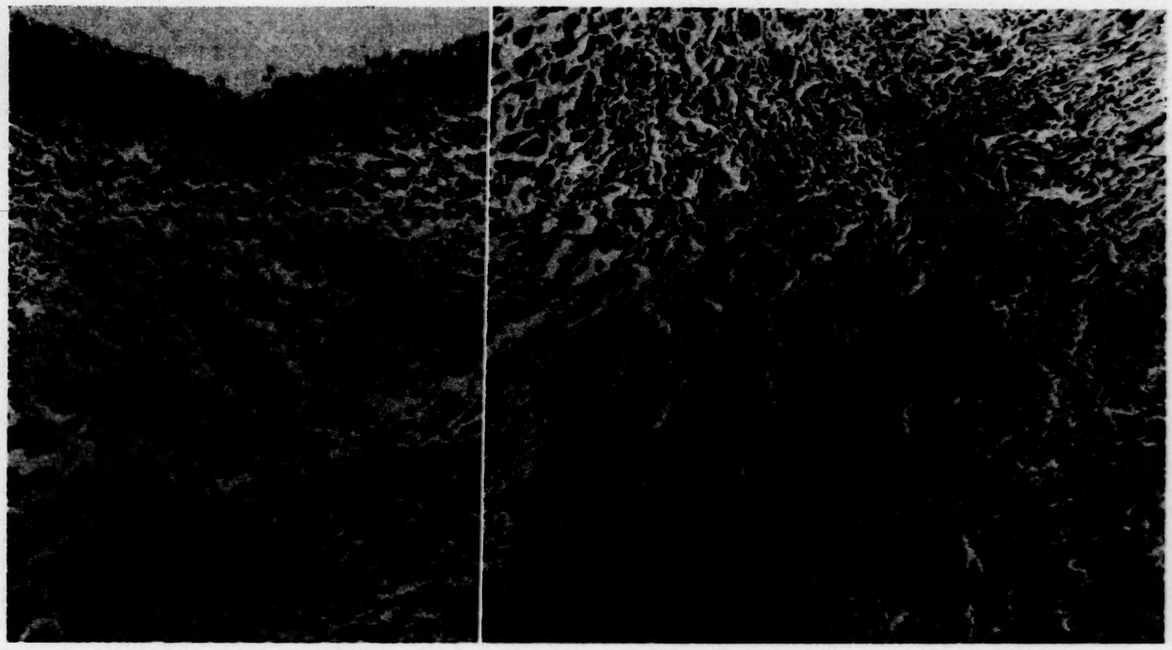

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FIG. 3. Pericardium, Case 1, showing fibrinous exudate, granulation tissue and multinucleated giant cells with phagocytosed fragments of collagen-like material; hematoxylin and eosin stain, × 950.

FIG. 4. Myocardium, left ventricle, Case 1. Destruction of the muscle fibers by the granulomatous lesion; hematoxylin and eosin stain, × 525.

typical changes of necrosis did not appear, it was believed that the patient had probably had a myocardial infarction and dicumarol therapy was reinstituted.

During the next three weeks the patient also had left pleural pain at times associated with a pleural rub and occasional fever to 102°F. During the tenth hospital week, however, an area of suppuration of the left buttock was incised and drained of copious amounts of pus and her temperature rapidly returned to normal where it remained. During the next six weeks there was marked clinical improvement; her arthritis and episcleritis were quiescent and she was able to sit up in a chair and take a few steps in the walker.

On December 5, 1951, in her sixth hospital month, she suddenly complained of headache, became nauseated and vomited. Shortly thereafter she developed precordial pain radiating through to the back, which was pleuritic in nature but not accompanied by a cough. On physical examination she appeared to be acutely ill. Her blood pressure was 90/60; there was a tachycardia of 120; gallop rhythm was present; no pericardial or pleural friction rubs were heard. The pain continued despite large doses of narcotics. In three hours her temperature rose to 103°F. There was a leukocytosis of 17,500 with a normal differential. An electrocardiogram showed some slight S-T segment elevation in the precordial leads. A blood culture was sterile. Despite supportive therapy she lapsed into coma and died five hours after onset of the precordial pain.

Autopsy was performed fifteen hours postmortem. The external stigmata of Cushing's syndrome and the deformities of rheumatoid arthritis were apparent. In the pleural cavity there were dense adhesions and yellow loculated fluid, some of gelatinous and some of serous consistency. The pericardium contained more than 350 cc. of bloody fluid under so much tension that it appeared to have caused cardiac tamponade. Fibrinosanguineous exudate was layered upon an old adhesive pericarditis which enveloped the small heart. There were no gross deformities of the valves. Near the apex was a poorly demarcated area of scarring which extended into the interventricular septum. Over this area a mural thrombus was loosely attached to the thickened endocardium. Throughout the flabby myocardium there was diffuse fine fibrosis. The coronary arteries were completely

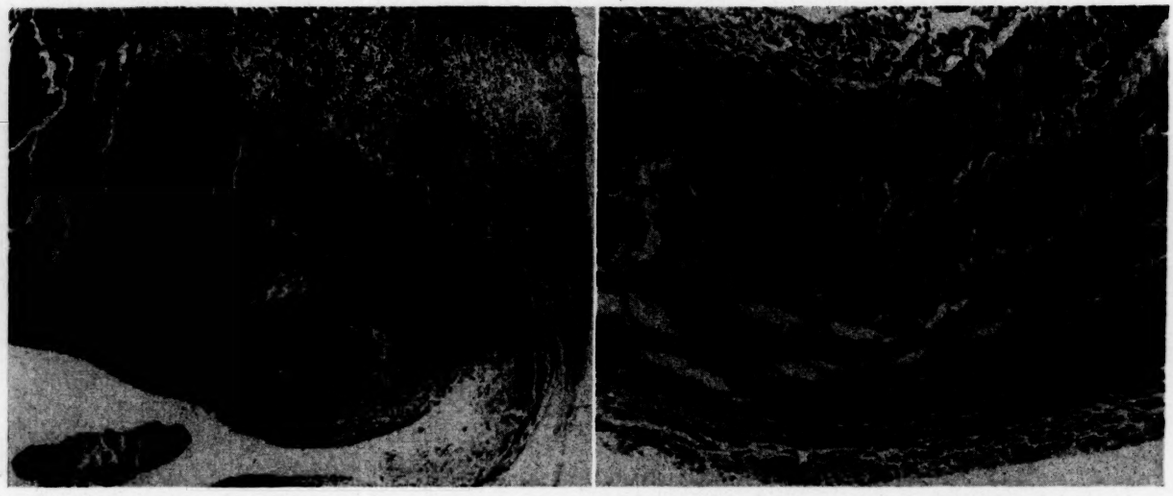

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FIG. 5. Mitral valve, Case 1. Areas of necrosis surrounded by granulomatous response. Giant cells at periphery of necrosis similar to those seen in pericardium; hematoxylin and eosin stain, × 50.

FIG. 6. Aortic valve, Case 1; entire thickness. Note similarity to pericardial and mitral lesions; hematoxylin and eosin stain, × 600.

free of gross atheromatous lesions. A few fibrous adhesions were present beneath a surgical scar and about the spleen. The kidneys were symmetrically contracted. Both presented ill defined, pale, triangular areas with the apex at the papillae. The adrenals were atrophic and friable. The sternoclavicular and right knee joint were explored. The synovia was thick and edematous and the articular surfaces of the joints were roughened. Culture of the pericardial fluid yielded B. proteus and enterococcus. The gross examination was otherwise not remarkable.

Microscopically, the lesions of the pericardium presented a bizarre picture. (Fig. 3.) The fibrinous exudate on the surface overlay a layer of granulation tissue richly infiltrated with polymorphonuclear cells, lymphocytes and large mononuclear cells resembling histiocytes. Necrosis of collagen fibers occurred in the fibrous tissue deep to the granulation tissue and was attended by huge multinucleated giant cells which phagocytosed large particles of collagen-like material. Small arteries in the epicardial fat showed necrosis of the wall and an occasional thrombus.

Sections through the pericardial reflection at the base revealed extension of the lesion into the epicardial fat on one side and the myocardium on the other. This was characterized by coalescing granulomatous nodules with centers of necrotic cellular débris or amorphous fibrinoid material exhibiting polychromatic staining which varied from brilliant pink to dull purple in hematoxylin and eosin preparations. (Fig. 4.) About the necrotic central areas giant cells and proliferating fibroblasts similar to those in the pericardium assumed a radial and palisaded appearance. Throughout this area and about the periphery of the nodule were polymorphonuclear cells, lymphocytes and histiocytes. The coalescence of nodules could be traced, as well as all stages of development and regression.

The lesions of the mitral and aortic valves belied their innocent gross appearance. It was apparent that the process had damaged the valve rings and had extended from this area to destroy the adjacent myocardium and the valve substance. At the line of closure in the mitral valve there was a necrotic mass penetrating the entire thickness of the valve. (Fig. 5.) The main artery at the base of the valve was involved in the lesion of the ring. Both the ventricular and sinus surfaces of the aortic valve were covered by an exudate similar to that of the pericardium. (Fig. 6.) The process ended abruptly at the sinus of Valsalva. The disintegration of collagen, the giant cell formation and palisading were striking.

Over the endocardium of the left ventricle was a laminated thrombus of varying age undergoing organization. A diffuse myocardial fibrosis but no areas of acute necrosis were present. There were evidences of recanalized lumens in several of the branches of the coronary artery.

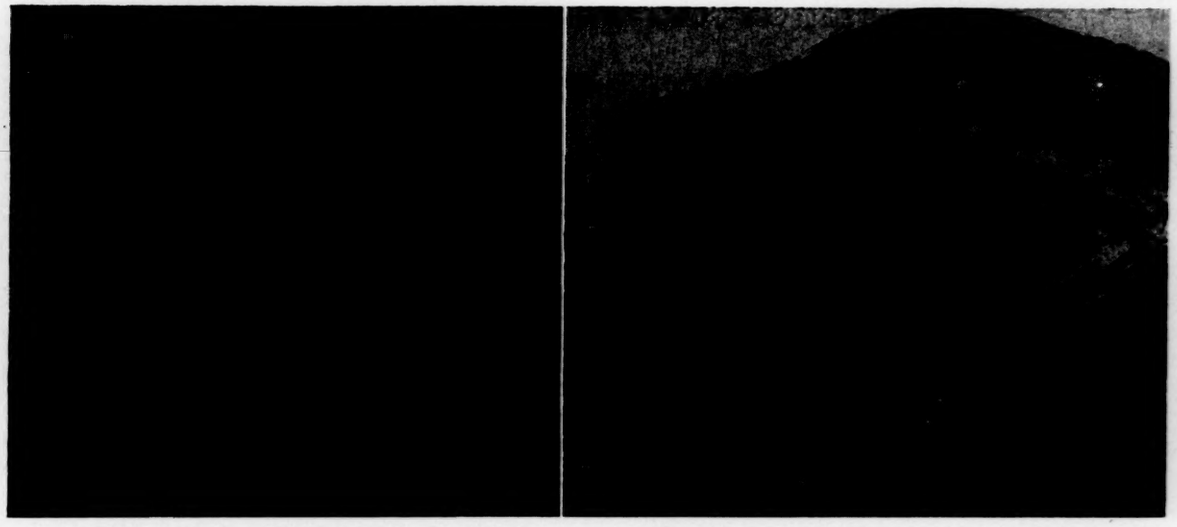

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FIG. 7. Granuloma in cortex of kidney, Case I; hematoxylin and eosin stain, × 450.

FIG. 8. Synovia, Case I. Large area of necrosis surrounded by granulomatous reaction similar to lesions in mitral valve; hematoxylin and eosin, × 40.

Aschoff bodies were absent in sections of the myocardium. The tricuspid valve was normal. The epicardial exudate was thick over the posterior wall and the abundant subepicardial fat was infiltrated with polymorphonuclear cells.

The pleura was thickened by dense connective tissue. Over the surface was an exudate similar to that of the pericardium. The alveolar spaces were compressed beneath this but otherwise the parenchyma appeared normal.

The liver, spleen and pancreas were not remarkable except for mild fatty changes in the liver. The kidneys showed lesions typical of necrosis of the renal papillae. There was a notable lack of cellular response in the surrounding parenchyma. With Brown-Brenn stains gram-positive cocci were visualized in the papillae. In addition there was fine cortical scarring with a lymphocytic infiltration of the interstitium. The convoluted tubules contained hyalin casts while in the collecting tubules were large amounts of calcium in the epithelium and in the lumens. A small concretion was attached to one of the papillae. Scattered through the cortex were occasional small granulomatous lesions similar to those seen in the myocardium. (Fig. 7.)

The adrenals had a thickened capsule and the cortical cells were disarranged. The cortex was extremely thin although the cells appeared to contain abundant lipid. The thyroid was atrophic. The lamina propria of the esophagus was thick and edematous. It was infiltrated by polymorphonuclear cells, plasma cells and lymphocytes but no specific granulomatous lesions could be identified. The remainder of the gastrointestinal tract was normal except for diverticulosis of the colon. The synovia of the knee joint showed lesions in every way similar to those described in the heart and as severe. (Fig. 8.) Sections of the pectoral and abdominal muscles revealed a few small foci of lymphocytes and plasma cells about the small blood vessels.

In summary, the systemic lesions presumably related to rheumatoid arthritis in this case were: pancarditis, pleurisy, synovitis and the granulomatous lesions of the kidney.

CASE II. (Fig. 9.) M. S., a forty-six year old, single, white secretary was admitted to Goldwater Memorial Hospital in October, 1951, for the treatment of rheumatoid arthritis.

The patient had had urticaria pigmentosa since the age of nineteen years. At twenty-five she had the onset of grand mal type of idiopathic epilepsy with seizures controlled by phenobarbital and mesantoin. At the age of thirty-one she developed joint pain with swelling and limitation of motion involving successively her shoulders, temperomandibular joints, and proximal interphalangeal and small joints of the feet. The diagnosis of rheumatoid arthritis was made and she was treated with diathermy and injections of unknown type without improvement. During the next five years she became progres-

sively more incapacitated and was unable to work. In 1939 she was admitted to the Columbia Research Division of the Metropolitan Hospital. Pertinent findings at that time included generalized urticaria pigmentosa, fusiform fingers and symptomatic improvement. In November, 1950, she was started on cortisone therapy with a final maintenance dose of 125 mg. per day. Although there was some relief of the joint pain and stiffness at time of discharge from the hospital in

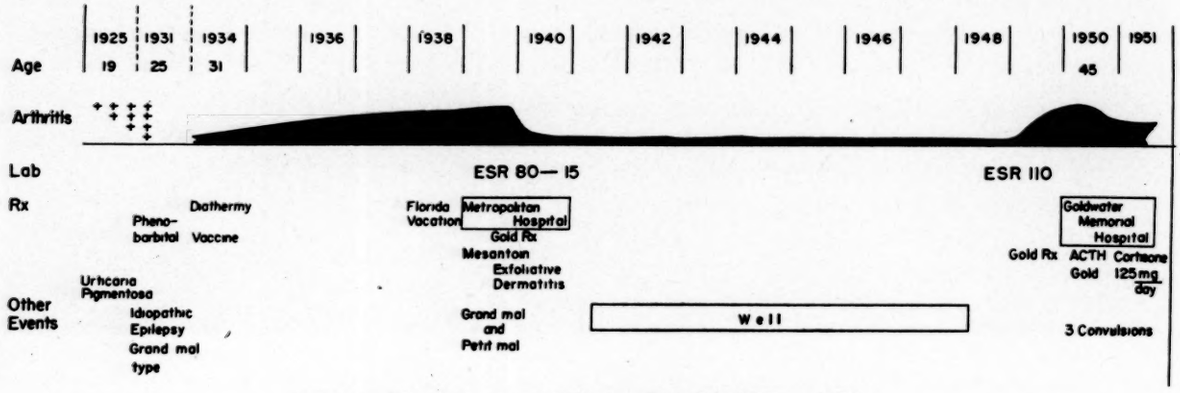

FIG. 9. Clinical course of Case II (M. S.) 1925 to 1951.

impaired motion of fingers, wrists and knees. The heart was not enlarged; there was an apical systolic murmur. Hemoglobin was 68 per cent; erythrocyte sedimentation rate was 80 mm. in one hour (Westergren); serum agglutinated group A hemolytic streptococci. Typical joint changes of rheumatoid arthritis were found by x-ray. She received two courses of intramuscular gold therapy. Following the second course there was a dramatic remission of the arthritis and she was able to move about with complete freedom although some residual deformity of her hands persisted. She returned to work as a secretary and remained well until 1949 when, without a known precipitating event, her rheumatoid arthritis relapsed.

She was admitted to the Columbia Research Division of the Goldwater Memorial Hospital in January, 1950, for the treatment of rheumatoid arthritis. She was semi-ambulatory, with typical rheumatoid deformities of the extremities but without subcutaneous nodules. An apical systolic cardiac murmur was present and the spleen tip was palpable. Hemogram was normal except for hemoglobin of 9.8 gm. per cent. The erythrocyte sedimentation rate was 100 mm. in one hour (Westergren). The agglutination test with group A hemolytic streptococci was positive. X-ray evidence of rheumatoid arthritis of the metacarpal, phalangeal, interphalangeal and knee joints was present.

She was treated initially with several short courses of corticotropin with good temporary

July, 1951, the patient was able to walk only a few steps with crutches.

Between July, 1951, and October, 1951, the patient was maintained at home on oral cortisone therapy, receiving 125 mg. per day. She was able to walk with canes only with great difficulty. In August, 1951, two grand mal seizures were followed by pain in the thoracic vertebrae. Compression fracture of D 6-8, D 10, and L 4 and 5 were demonstrated by x-ray. In October, 1951, the patient was readmitted to the Columbia Research Division of Goldwater Memorial Hospital because of the vertebral fractures and increased activity of her rheumatoid arthritis.

Physical examination showed temperature 100°F., pulse 102, respiration 24, blood pressure 124/78. Generalized urticaria pigmentosa and a Cushing-type facies were noted. A pleural friction rub was heard in the left axilla. There were signs of fluid at the left base. The left cardiac border was 1 cm. outside the midclavicular line in the sixth intercostal space. A grade II systolic murmur was heard over the entire precordium. The tip of the spleen was palpable. Obvious rheumatoid deformities of the hands, knees, elbows and shoulders and subcutaneous nodules over the right olecranon process were present.

Hemoglobin was 11.5 gm.; white blood cell count was 10,800 with a normal differential. The erythrocyte sedimentation rate was 43 mm. in one hour. Chest x-ray showed thickened pleura at the left base. Oral cortisone therapy

was started; the initial dose was 75 mg. per day; this was increased in one week to 125 mg. per day by which time the pleuritic pain disappeared.

X-rays of the spine shortly after admission showed severe generalized osteoporosis and multiple compression fractures of the vertebrae (D 6, 8, 12 and L 2 and 5). The serum calcium, phosphorus, alkaline phosphatase and urine calcium values were normal. In December, 1951, the patient had a grand mal convulsive seizure during which she sustained fractures of the left hip and right knee. She was treated with splints and traction. In an attempt to arrest the severe osteoporosis she received testosterone (25 mg. per day), stilbestrol (1 mg. per day), calcium lactate (2 gm. per day) and strontium lactate (7½ gm. per day).

In January, 1952, she again developed pleuritic pain accompanied by a pleural friction rub over the left axilla. There were clinical and x-ray signs of consolidation of the left lower lobe but there was no fever. In the next few days effusion developed at the left base. Thoracentesis yielded 50 cc. of yellow fluid, specific gravity 1.008, 317 cells/mm., 50 per cent polymorphonuclear leukocytes. Cultures were negative for organisms including tubercle bacilli. During this same period her cortisone dosage was reduced to 75 mg. per day. One week later the patient complained of substernal pain and a pericardial friction rub was heard. There was a fall of blood pressure to a low of 85/65; clinical and radiographic signs of pericardial effusion and electrocardiographic changes consistent with those found in pericarditis were present. Concomitantly right-sided pleural pain and friction rub with temperature elevation to 102°F. occurred. It was believed that the pleurisy and pericarditis might represent visceral components of the rheumatoid process. Accordingly, the cortisone dosage was increased to 125 mg. per day. During the ensuing weeks signs of increasing pericardial effusion developed; these diminished only after the cortisone dosage was increased to 200 mg. per day. There was a transient episode of auricular fibrillation. In February, 1952, an area of pressure necrosis first appeared on the posterior chest wall. In the ensuing ten months she developed multiple suppurating wounds of her buttocks, hips and back. Between March and April, 1952, the dosage of cortisone was gradually decreased from 200 mg. per day to 50 mg. per day because of osteoporosis and multiple foci of cutaneous infection. During this period of lowered cortisone dosage there was no flare-up of arthritis or pleuritis.

In May, 1952, because of arthritic pain, the patient received butazolidin® for one month without demonstrable effect on her status. In July, 1952, butazolidin and cortisone were discontinued and she received corticotropin gel, 40 U. per day, for one month without effect. After cessation of the corticotropin no arthritic flare-up appeared although cortisone was not reinstituted. Her subsequent course was marked by severe malnutrition despite a high-caloric diet and supplemental protein feeding. Her decubiti became the major problem. She ran a constant low-grade fever which was attributed to the inflamed decubiti and occasional urinary tract infections.

In September, 1952, generalized anasarca appeared, with a fall in serum albumin to 2.8 gm. per cent. A nodule appeared in the right sclera which cleared with local cortisone application. The decubiti continued to spread despite débridement and local and systemic trial of many antibiotics. Cultures revealed mainly B. proteus. Large amounts of analgesics were necessary to control pain due mainly to the decubiti which involved most of the posterolateral surfaces of the trunk. She developed an increasingly loud systolic murmur at the apex of the heart without clinical enlargement of the heart or signs of congestive heart failure. The possibility of bacterial endocarditis was considered. No petechiae or hematuria were noted and blood cultures remained sterile. The patient had transient bouts of irrationality, became increasingly comatose and expired November 28, 1952.

Autopsy was performed eight hours postmortem. The body was wasted. Numerous 2 to 5 mm. brown pigmented areas were evident over the trunk. Huge decubiti with extensive undermining and sinus formation were present over the hips, thorax and sacrum. These exuded a foul pus. The rib cage was extremely fragile. The pleural cavity was obliterated by dense fibrous adhesions. No fluid was present but flecks of fibrin were seen as the adhesions were severed. The lungs were small and crepitant except for several small circumscribed yellow nodules about 3 mm. in diameter deep in the parenchyma of the left upper lobe which were soft and necrotic. In addition, this lobe contained a solitary firm subpleural tubercle of the same diameter.

FIG. 10. Mitral valve, Case II. Section through the large vegetation. Destruction of the valve ring and extension into myocardium is seen at the left. In the center there is adhesion to a trabecula carnea of the left ventricle. The destruction of a chorda tendinea and the adjacent areas of the papillary muscle are seen at the right; hematoxylin and eosin stain, × 10.

The pericardial sac was also obliterated by fibrous adhesions and was free of fluid. The heart weighed 150 gm. The tricuspid, pulmonary and aortic valves appeared normal grossly. The mitral valve was puckered and stenotic due to the presence of a large yellow vegetation covered with fibrin which extended from the posterior leaflet onto the anterior leaflet, downward onto the chordae tendineae but did not appear to involve the auricular endocardium. In its greatest dimensions the vegetation measured 1.5 by 1 by 2 cm. and at its base appeared to be partially covered by endocardium. (Fig. 10.) The uninvolved chordae of the anterior leaflet were thin and delicate and presented no evidence of pre-existing rheumatic lesion. The myocardium was uniformly dark brown and flabby. Dense adhesions bound the liver and spleen to the abdominal wall and the diaphragm. The liver weighed 1,600 gm. but was otherwise not remarkable. The spleen was enlarged, weighing 300 gm. and firm. The adrenals contained numerous small adenomas. The kidneys showed a few flat scars. The mediastinal lymph nodes were small and discrete. There was a severe scoliosis as well as the generalized rheumatoid deformities of the joints of the extremities. The right femoral head and lumbar vertebrae seemed exceedingly soft and the cortex thin. The synovia of the hip joint was edematous and congested.

Microscopically, the tubercle in the left upper lobe was hyalinized. The yellow nodules seen grossly did not resemble tuberculosis. Their centers were necrotic. (Fig. 11.) About the periphery were occasional giant cells and small, more immature granulomas which also had necrotic centers surrounded by nuclear dèbris, bizarre spindle-shaped cells, lymphocytes, histiocytes and polymorphonuclear cells. (Fig. 12.) Fibrinoid material filled the alveolar spaces. Acid-fast and bacterial stains of these lesions were negative for organisms.

Both the pleura and pericardium varied in thickness with the adhesions. Small fibrinous deposits on the surface were accompanied by lymphocytic and histiocytic infiltrations.

The most striking lesion occurred in the mitral valve. Sections of the area surrounding the large vegetation showed extension of the lesion from the mitral ring. The appearance was identical with that of Case I but the destruction was greater. The lesion consisted of necrosis of the collagenous tissue with palisading of bizarre spindle-shaped cells and infiltration of lymphocytes, polymorphonuclear cells, Anitschkow myocytes, giant cells and nuclear débris. All stages of the lesion could be traced, from incipiency to scarring. The process assumed both a nodular form in the valvular substance and a linear form as it spread over the endocardial

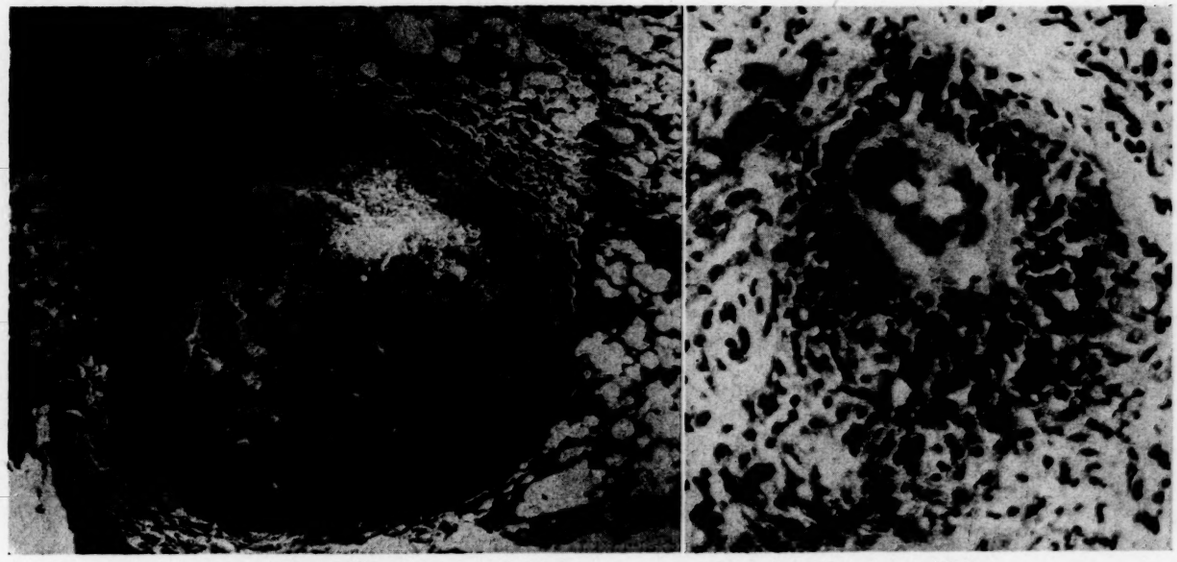

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FIG. 11. Nodule in parenchyma of left upper lobe of lung, Case II. The large area of central necrosis is surrounded by alveoli filled with fibrinoid material. Numerous small granulomas are present about the periphery of the large nodule.

FIG. 12. Lung, Case II. A small lesion in periphery of large nodule. Note the necrotic center and surrounding cellular exudate. These are typical of small nodules which coalesce to form the large lesions; hematoxylin and eosin stain, × 744.

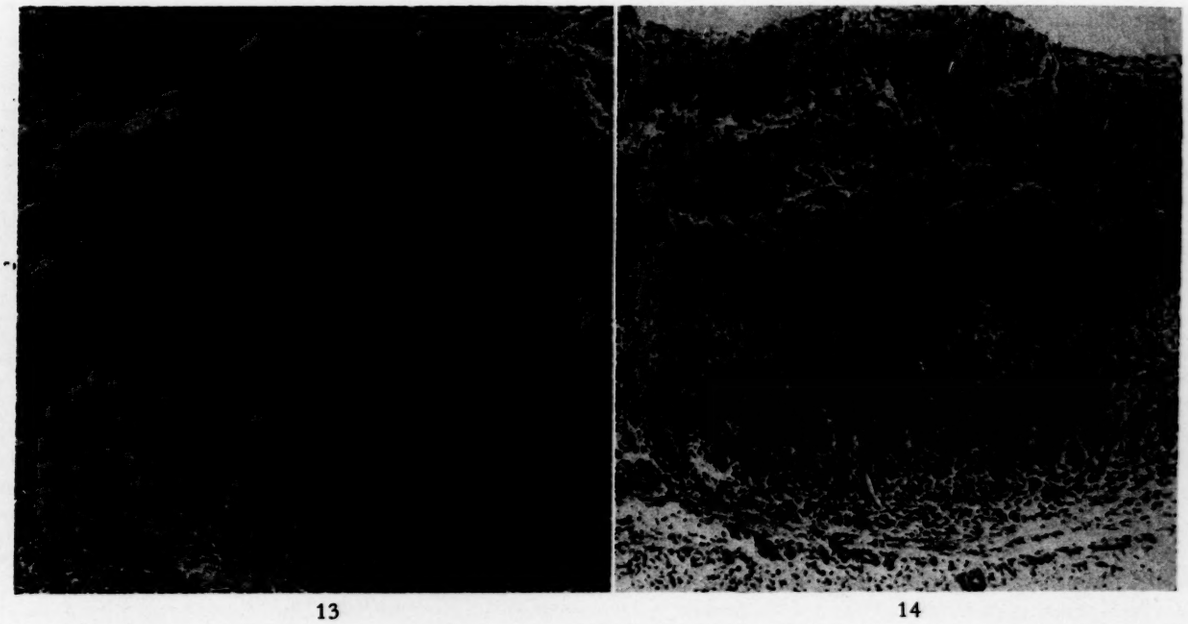

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FIG. 13. Myocarditis, Case II. The central areas consist of fibers giving the staining reactions of collagen and have few nuclei. They are surrounded by a cellular exudate and proliferating fibrous tissue. These lesions appear older than the nodules with the necrotic centers; hematoxylin and eosin stain, × 120.

FIG. 14. Aortic valve, Case II. Full thickness of valve showing cellularity and palisading of fibrocytes about fragmented collagen fibers. Note similarity to lesion in Case I, Figure 6; hematoxylin and eosin stain, × 100.

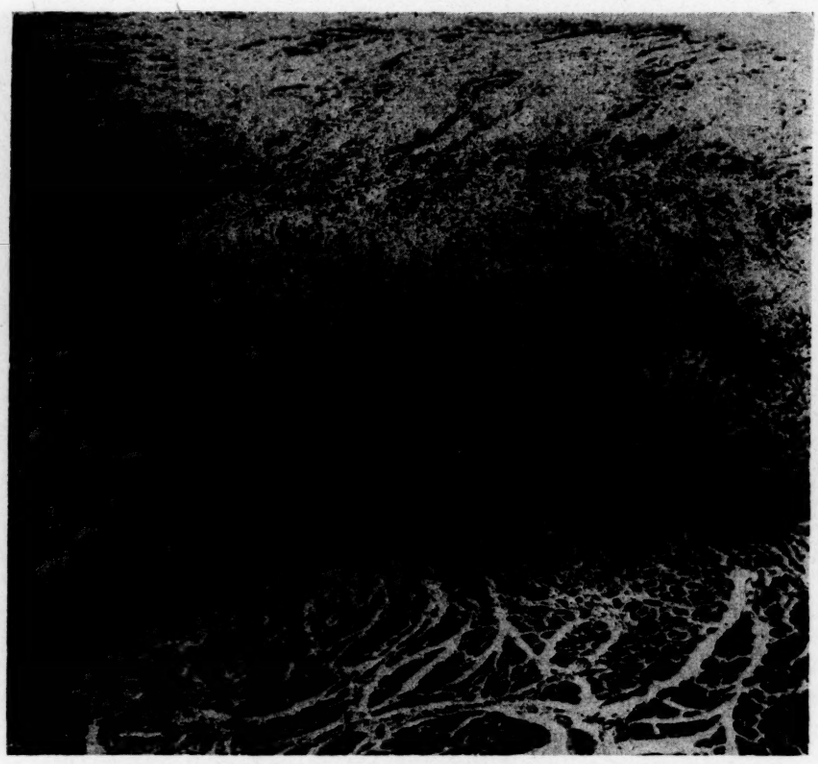

FIG. 15. Diaphragm, Case II. Granulomatous lesion deep to pleural surface with extension to muscle and intramuscular connective tissue septa. The dark strands just above the muscle are areas of fibrinoid necrosis; hematoxylin and eosin stain, × 40.

surfaces to involve the chordae tendineae. The papillary muscle was replaced by the granulomatous lesions from the endocardial surface as was the myocardium of the ventricle by extension from the mitral ring. (Fig. 13.) The large vegetation of the mitral valve was similar except for its size and the extensive necrosis. The aortic, tricuspid and pulmonary valves despite their normal gross appearance showed similar lesions. Those in the aortic valve (Fig. 14) had the appearance of older lesions apparently going on to fibrosis and hyalinization. In all instances the lesion seemed to be initiated in the ring and along the mesothelial surfaces and to extend from there into the myocardium. No Aschoff bodies were demonstrable. Bacteria could not be visualized by Brown-Brenn or Ziehl-Neelsen stains.

Deep to the fibrous layer on the pleural surface of the diaphragm was an ill defined zone of necrosis and granulomatous lesions which penetrated and destroyed the muscle. (Fig. 15.) The lesion extended along the connective tissue septa and thus deep into the muscle but the peritoneal surface, though thickened by fibrous tissue, showed no necrotic foci. The synovial surfaces and tendons of the right (unfractured) hip were the sites of similar severe lesions. (Figs. 16 and 17.)

The esophagus showed normal epithelium and a diffuse perivascular infiltration of plasma cells, lymphocytes and an occasional eosinophil. The muscularis was normal but over the serosal surface was a reaction similar to that of the pleura and pericardium.

The liver contained an unidentified brown pigment that was negative for strontium, iron, ceroid and gold. There was mild chronic passive congestion of the liver and of the spleen. The kidneys showed a moderate degree of non-specific scarring and lymphocytic infiltration of the interstitium. The renal pelves and blood vessels were normal. The lymph nodes of the mediastinum showed only non-specific chronic lymphadenitis. There was osteoclasis of the rib but only osteoporosis of the femur. The vertebral bodies through the fracture sites showed almost no calcification of the scanty osteoid tissue. The skin and subcutaneous tissues from the decubiti showed a non-specific inflammatory reaction.

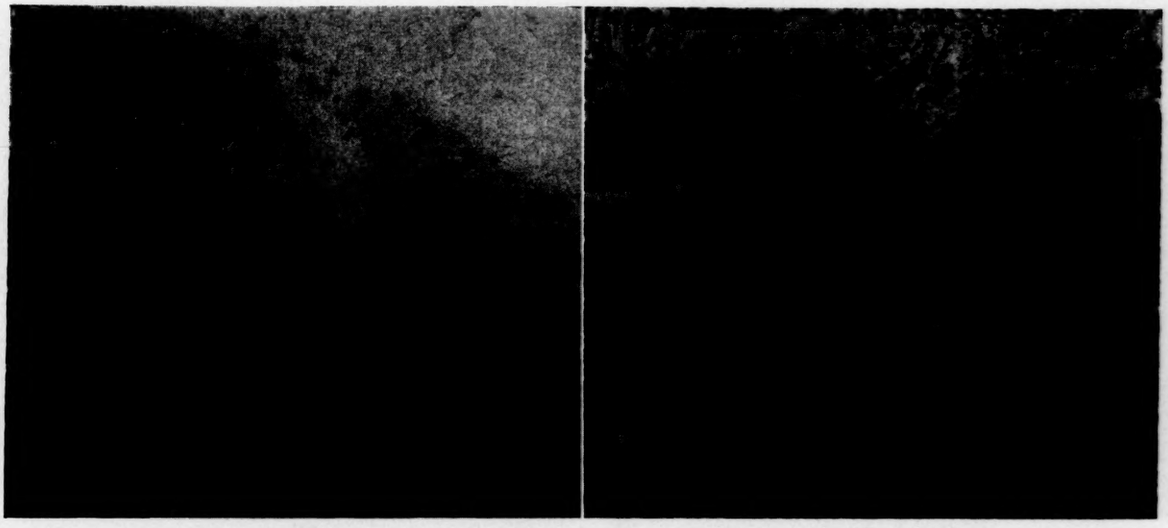

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FIG. 16. Lesions in intracapsular ligamentous attachments of right hip, Case II. Note subendothelial destruction and cellular infiltration of wall of small arteries at bottom of section; hematoxylin and eosin stain, × 120.

FIG. 17. Synovia, Case II. Bizarre cells and fibrinous exudate on surface; hematoxylin and eosin stain, × 120.

In summary, the systemic lesions presumably related to rheumatoid arthritis in this case were: pancarditis, pleurisy, diaphragmatitis, granulomas of lungs and synovitis.

COMMENTS

It is apparent that a malignant form of rheumatoid arthritis was largely responsible for the deaths of these two patients. The clinical course in each patient has certain similar features. In both individuals there was evidence of an inflammatory process in pleura, pericardium and myocardium; generalized osteoporosis with fractures while on cortisone therapy; severe and progressive synovitis and finally an overwhelming breakdown of the integument. Episcleritis occurred in both during the period of deterioration and cleared rapidly on local cortisone therapy. Both patients had intensified activity of their articular and visceral disease when cortisone therapy was reduced or discontinued, except in Case II in the terminal state. Anatomically, both patients had extensive lesions of the pleura, pericardium and synovia. With the exception of the diaphragmatic surface of the pleura in Case II, the lesions in these areas in Case I appeared more acute and fulminating. However, the deformity of the mitral valve by the huge vegetation and the panvalvulitis was more severe in Case II. The diaphragmatic and pulmonary lesions do not correspond with the somewhat non-specific changes noted by Ellman and Ball.[5] Both patients had an esophagitis. This could not be adequately explained since the epithelium was intact. Only one of the patients had been tube-fed (Case II). The esophagitis was therefore believed to be an extension of the process from the serous surfaces of the mediastinum though the inflammatory reaction showed no specific granulomatous lesions.

The information obtained from observation of these two patients afforded an opportunity to study the evolution of the primary lesion since all stages of development and regression could be traced. The nidus is a fibrinoid necrosis of the vessel wall beginning in the subendothelial layer (Fig. 18) from which fibrinoid material extends to the surrounding tissue. Concomitantly there is an infiltration of polymorphonuclear neutrophils, eosinophils, lymphocytes and histiocytes in the vessel wall and about the fibrinoid material. The endothelial cells are swollen. Several of these small lesions coalesce to form small nodules with necrotic centers and proliferating granulation tissue arranged in a zone about them. The lesions appear indistinguishable from the subcutaneous nodules of rheumatic disease described by other authors.[6,7]

Questions may be raised concerning the presence of subacute bacterial endocarditis in Case II. Only negative evidence against the diagnosis can be offered: (1) negative blood cultures and absence of embolic phenomena antemortem, (2) no organisms could be stained

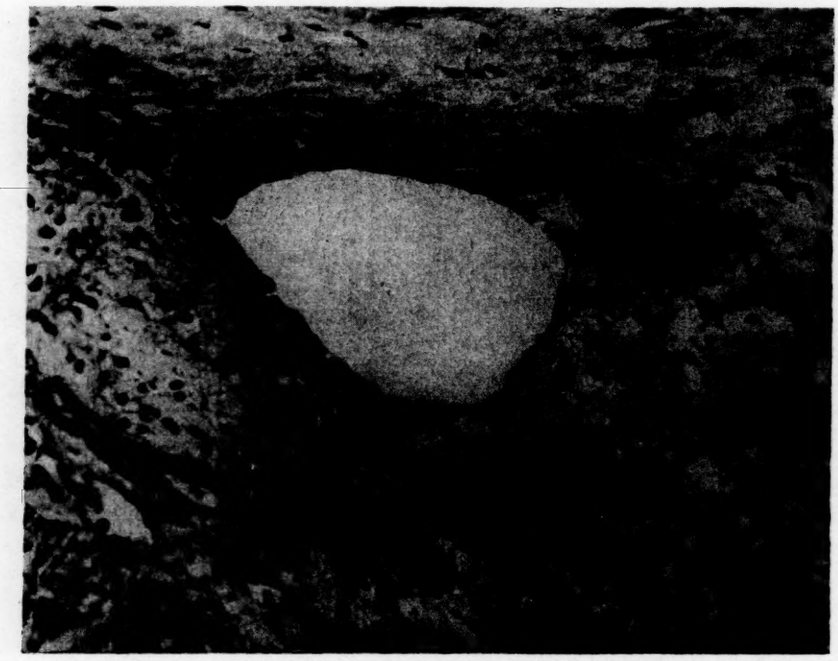

FIG. 18. Early vascular lesion in small blood vessel presumably an artery, Case II. Note intact swollen endothelium, cellular infiltration, and fibrinoid necrosis represented as irregular black area at right extending into adjacent tissue. This is typical of the earliest lesions found; hematoxylin and eosin stain, × 360.

within the lesions, (3) no infarcts or focal embolic lesions were found in the kidney, (4) all four valves were involved—a most unusual circumstance in subacute bacterial endocarditis and (5) no Bracht-Wächter bodies were encountered in the myocardium.

In Case I the question of terminal bacteremia arises in that the pericardial fluid grew out enterococcus and proteus on culture. Both the decubiti and kidneys could have been the source of the infection but again the chronicity of the cardiac lesion belies this origin.

The high incidence of cardiac lesions found at necropsy in rheumatoid arthritis has been mentioned by numerous investigators. Baggenstoss and Rosenberg[1] found fourteen of twenty-five cases with lesions which they considered indistinguishable from rheumatic fever. In an extension of their series[2] sixteen of thirty were classified as having rheumatic cardiac lesions and two additional cases were considered doubtful. Graef, Hickey and Altmann[3] reviewed sixty-six cases of rheumatoid arthritis and found nineteen with mild valvular deformity, one with mitral stenosis and five with "old rheumatic valvulitis"; thirty-three had pericarditis. In their series there were two which showed "granulomatous lesions of interstitial collagenous necrosis indistinguishable from those seen in rheumatoid subcutaneous nodules." Gruenwald[8] reported a case of rheumatoid arthritis with cardiac and visceral lesions similar to ours, and Raven, Weber and Price[11] reported a patient with visceral and myocardial necrobiotic nodules.

The absence of a history of acute attacks of rheumatic fever in these reports of rheumatoid arthritis is noteworthy. Furthermore, clinical signs of rheumatic heart disease were absent in the majority of patients subsequently found to have valvular deformities at autopsy. These were usually slight. It seems entirely probable that the high postmortem incidence of rheumatic valvulitis reported in rheumatoid arthritis represents the healed stage of the lesion which we have encountered in its fulminating state.

Visceral lesions in rheumatoid arthritis have been studied by others.[2,8,9] A high incidence of fibrous pleural adhesions has been encountered but only Gruenwald has reported the presence of active granulomatous lesions in the pleura as well as in the capsule of the spleen. Kidney lesions in the form of glomerulitis described by Bell[10] were not seen by us. A non-specific type of interstitial scarring, however, was observed in both our cases in addition to the granulomatous lesions in Case I. It is possible that some of this

scarring may have been related to healed granulomatous lesions. The synovial lesions were active and assumed the same granulomatous character seen elsewhere.

It is our belief that this disease should be called malignant rheumatoid disease—not arthritis; that the valve rings and serous surfaces are particularly vulnerable and that the myocarditis is a direct extension of the inflammatory process; that it differs morphologically from rheumatic fever in the granulomatous character of its valvular myocardial lesion, in the lack of Aschoff bodies, and in the granulomatous visceral and synovial lesions. Furthermore, it is believed that milder forms of this disease in their healed state have been responsible for the valvular deformities heretofore ascribed to rheumatic fever and account for all except the few coincidental and documented cases of acute rheumatic fever that are apt to occur among any large number of cases of rheumatoid arthritis. In other words, the incidence of rheumatic heart disease is probably no higher in the rheumatoid arthritis population than in the general population. The obliterative pleuritis, chronic pericarditis and valvular deformities represent a distinct entity and should be attributed to rheumatoid disease. It is apparent that cortisone, corticotropin and butazolidin were of no avail in terminating this disease and perhaps abetted the osteoporosis and breakdown of the integument. It is impossible to be sure that the administration of these potent anti-inflammatory agents did not have a relationship to the fulminating character of the rheumatoid disease. It must be noted, however, that such severe widespread manifestations have not previously been seen by us and have been described in the past only in Gruenwald's report before the use of cortisone.

SUMMARY

The case histories of two patients with severe prolonged rheumatoid arthritis complicated clinically by pericarditis and pleurisy are presented. These patients received long-term cortisone therapy.

At postmortem examination necrotic and granulomatous lesions in all stages of evolution and healing were found in the pleura, pericardium, myocardium, endocardium, diaphragm, synovia, and in the kidneys and lungs. The primary lesion was fibrinoid necrosis of the wall of small blood vessels. Coalescence of several of these injured vessels and the inflammatory response resulted in a lesion indistinguishable from the rheumatic nodule.

Evidence is presented that there is a malignant form of rheumatoid "arthritis" which is a systemic disease. The relationship of this fulminating disease to the reported high incidence of rheumatic heart disease in patients with rheumatoid arthritis is discussed.

Long-term cortisone therapy apparently does not prevent the development of this form of rheumatoid disease.

Addendum: At the meeting of the American Rheumatism Association held in New York on May 28, 1953, several other cases of angiitis in patients with rheumatoid arthritis were presented by Drs. Robinson, Ogryzlo and Weinberger. The relationship of the drome to cortisone administration was discussed but left undecided.

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Phenylbutazone (Butazolidin) in Gout*

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DURING the past four years phenylbutazone has been employed extensively in the treatment of various rheumatic diseases. Many reports have been made concerning its therapeutic efficacy. The therapeutic effect in gout appears to be more beneficial and selective than that in other painful musculoskeletal disorders.

In an early report on irgapyrin® (a mixture of aminopyrin with phenylbutazone) Fenz[2] first noted a striking therapeutic effect in five patients with acute gout. In 1951 we reported similar benefit in a series of thirty patients treated with irgapyrin.[3] When phenylbutazone was made available separately, this beneficial effect was again observed.[4] Phenylbutazone was found to be as effective as the mixture (irgapyrin) but less toxic.

This report concerns the use of phenylbutazone in a group of 200 patients with acute gout and/or chronic gouty arthritis observed during a period of thirty months from November, 1950, to May, 1953. During the first eight months phenylbutazone was used with equal parts of aminopyrin in the mixture known in Europe as irgapyrin® and in the United States as butapyrin.®

CLINICAL EVALUATION

For the most part, phenylbutazone was administered orally in coated tablets of 100 or 200 mg. or in capsules containing 200 mg. It was given intramuscularly in a 20 per cent solution of its sodium salt or, because of pain at the site of injection, in combination with local anesthetics. The usual intramuscular dose was 1 gm. In the early months of this study oral daily dosage ranged from 100 to 1,600 mg. but later the average daily dose rarely exceeded 600 mg. The administration of phenylbutazone† in gelatine capsules or in coated tablets did not result in any appreciable difference in the therapeutic benefit or toxic effect.

Despite the published reports[5a,b] indicating a more rapid rise of blood levels of phenylbutazone following oral administration, we often observed more rapid clinical improvement after intramuscular administration. In the treatment of acute gout daily injection of 1 gm. for one to three days was usually sufficient for relief of symptoms.

TABLE I
SEX AND AGE DISTRIBUTION OF 200 GOUT PATIENTS

Decade	Males	Females	Total
3	4	..	4
4	22	..	22
5	41	11	52
6	41	12	53
7	24	15	39
8	23	5	28
9	1	1	2
	156	44	200

In Table I 200 patients with acute and chronic gout are classified according to sex and age in decades. As may be seen, there were 156 males and 44 post-menopausal females included in the study.

Table II demonstrates the therapeutic response of gout in 156 males. The gout patients were divided into two groups: Stage I (acute gout, with asymptomatic periods between exacerbations) and Stage II (acute gout superimposed upon chronic gouty arthritis). Stage I

† Phenylbutazone (3,5-dioxo-1,2-diphenyl-4-n-butylpyrazolidine) was synthesized by H. Stenzel in the laboratories of the J. R. Geigy Co. of Basel, Switzerland. The chemistry and pharmacology of this pyrazole have been reported elsewhere.[1]

* From the Department of Pharmacology and Therapeutics, Rheumatic Disease Study Group, Stanford University School of Medicine, San Francisco, Calif. Presented at the Eighth International Congress on Rheumatic Diseases, Geneva, Switzerland, August, 1953.

comprised fifty-nine patients and Stage II ninety-seven patients. All males with acute gout (Stage I) showed some measure of therapeutic benefit following administration of phenylbutazone whereas two males with chronic gouty arthritis were unimproved. Therapeutic response* was graded from I to IV, from complete remission in forty-eight hours or less to "no effect." As may be observed, patients with Stage I acute gout responded somewhat better than those with Stage II chronic gouty arthritis; that is to say 93 per cent of the patients in the acute category responded with major improvement or complete remission whereas only 86 per cent of the chronic gouty arthritics exhibited this degree of improvement.

TABLE II
THERAPEUTIC RESPONSE OF GOUT TO PHENYLBUTAZONE (156 MALES)*

Stage:	I	II	III	IV	Total
I (Acute)	38	17	4	0	59
II (Chronic)	36	47	12	2	97
Total	74	64	16	2	156

* Stage I—Acute gout, with asymptomatic periods between exacerbations. Stage II—Acute gout superimposed upon chronic gouty arthritis.

Therapeutic Response—Grade I: complete remission in forty-eight hours or less. Grade II: major improvement, indicating rapid decrease of signs and symptoms within forty-eight hours, but with slight persistence up to seven days following initial therapy. Grade III: minor improvement with analgesia and decreased swelling, but not complete remission, in spite of continued therapy. Grade IV: no effect.

In Table III are summarized the therapeutic results in forty-four female gout patients treated with phenylbutazone. There were nine patients with acute gout and thirty-five with chronic gouty arthritis. Five patients in the latter group showed no improvement. Among the females, as with the males, the patients with acute gout responded more favorably than those with chronic gouty arthritis. Among the females 89 per cent obtained a grade I or II therapeutic response; whereas the females with chronic gouty arthritis falling in the comparable therapeutic grades comprised only 63 per cent. In general, the males responded more favorably than did the females. Computation of all of the males in grades I and II of therapeutic response was 88.5 per cent as against 68 per cent in the similar groups among the females.

* See footnote to Table II.

Table IV shows the therapeutic response of gout to phenylbutazone in the combined group of 200 patients, both males and females. Here it is of interest that 84 per cent of those with acute gout (Stage I) showed a grade I or grade II response whereas only 7 per cent achieved minor or no improvement. In chronic gouty arthritis (Stage II) 80 per cent showed a grade I or II response, and 20 per cent a grade III or IV response.

TABLE III
THERAPEUTIC RESPONSE OF GOUT TO PHENYLBUTAZONE (FORTY-FOUR FEMALES)*

Stage:	I	II	III	IV	Total
I (Acute)	3	5	1	0	9
II (Chronic)	5	17	8	5	35
Total	8	22	9	5	44

* Legend—See Table II.

TABLE IV
THERAPEUTIC RESPONSE OF GOUT TO PHENYLBUTAZONE ACCORDING TO STAGE OF DISEASE (200 PATIENTS —MALES AND FEMALES)*

Stage:	I and II	III and IV	Total
I (Acute)	63 (93%)	5 (7%)	68 (100%)
II (Chronic)	105 (80%)	27 (20%)	132 (100%)
Total	168 (84%)	32 (16%)	200 (100%)

* Legend—See Table II.

In evaluating the therapeutic effect of phenylbutazone in other painful musculoskeletal disorders we followed 408 patients in whom uric acid determinations were made before treatment. These were non-gouty rheumatic patients. Of these 408 patients (Table v) eighty-four had elevated serum uric acid before treatment. It is interesting that only 37 per cent of these eighty-four patients showed a grade I or grade II improvement in the diseases for which they were being treated as compared with a grade I or grade II response in 168 (84 per cent) of the 200 patients treated for gout. There were 324 patients with a variety of rheumatic diseases whose serum uric acid was in the normal range prior to therapy with phenylbutazone.

Of these 56 per cent showed a grade I or II response following phenylbutazone. This comparison is presented to emphasize that the previously reported effect of phenylbutazone in lowering serum uric acid in gouty and other patients may not be the most important pharmacologic action of the drug. In fact, in the group of 408 patients without gout the beneficial response was markedly less among those who had elevated serum uric acid prior to therapy than among those whose serum uric acid was normal.

TABLE V
THERAPEUTIC RESPONSE TO PHENYLBUTAZONE IN RHEUMATIC DISEASES OTHER THAN GOUT (408 PATIENTS)*

Serum Uric Acid	I and II	III and IV	Total
Elevated (above 5.5 mg. %)	31 (37%)	53 (63%)	84 (100%)
Normal (2.5 to 5.5 mg. %)	182 (56%)	142 (44%)	324 (100%)

* Grade I: complete remission; grade II: major improvement; grade III: minor improvement; and grade IV: no benefit.

In the typical case of acute gout given intramuscular phenylbutazone, relief of pain, swelling and erythema of the affected part was manifest occasionally in less than one hour and in many instances within several hours. The extent of relief experienced by most patients exceeded in degree and rapidity that which they had previously obtained with colchicine and/or hormone therapy. Relief was also achieved after the oral administration of phenylbutazone; in many instances the use of even small doses (i.e., 200 to 400 mg. daily) was followed by rapid subsidence of acute symptoms. It has been our usual procedure in the acute exacerbation of gout to administer 1 gm. phenylbutazone intramuscularly, followed with 400 to 800 mg. per day by mouth. Although we are of the impression that the intramuscular administration of phenylbutazone in acute gout is more effective than the oral, this has not been subjected to critical analysis by controlled studies.

Maintenance Therapy in Chronic Gouty Arthritis. In the treatment of gouty arthritis we were impressed by several responses. The attack rate was greatly reduced among those patients receiving phenylbutazone daily; patients who had experienced attacks at a rate of four to six times per year were able to avoid exacerbation in almost all instances during adequate maintenance therapy for periods up to two years. The severity of exacerbation in most instances was much less during maintenance therapy with phenylbutazone than with colchicine and salicylates. Furthermore, the rapidity with which exacerbation was controlled was much greater than with colchicine and/or salicylates. The acute exacerbations in chronic gouty arthritis could be checked by augmenting the daily maintenance dose with 200 to 600 mg., and incipient attacks could rapidly be aborted. The daily maintenance dose generally effective was found to be 200 to 600 mg. In several instances effective prevention of acute exacerbation in patients with severe tophaceous gout was possible with maintenance dosage of as little as 100 mg. per day. It is interesting that in these patients given 100 mg. of phenylbutazone per day the serum uric acid did not decrease markedly from the pretreatment level in spite of effective control of symptoms and prevention of acute exacerbation. The possible decrease in the "uric acid pool" during maintenance therapy remains to be evaluated. Despite the prolonged control of the gouty arthritic patients, we have in no case observed diminution in size of tophi although, on the other hand, they did not increase in size.

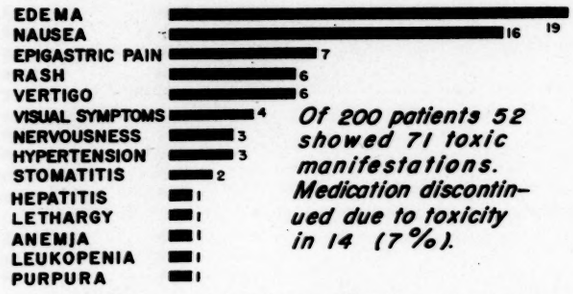

FIG. 1. Frequency of toxic manifestations in gout patients treated with phenylbutazone.

Toxicity. The toxic side effects produced by phenylbutazone are well known. It has been our experience in treating patients with a variety of rheumatic diseases that the group with gout has been outstanding in its relatively low incidence of toxic reactions to phenylbutazone. The gouty patient, nonetheless, is not immune to the various untoward effects which are represented in Figure 1 according to their incidence of occurrence as follows: edema, nausea, epigastric pain, rash, vertigo, visual symptoms, nervousness, hypertension, stomatitis, hepatitis, lethargy, anemia, leukopenia and purpura. It may be seen that edema is the most frequently

encountered side reaction and nausea is second in frequency. It will be noted that hematologic reactions are relatively rare; in fact, all three of the transient reactions observed occurred in the same malnourished alcoholic female. To date there has been no case of agranulocytosis

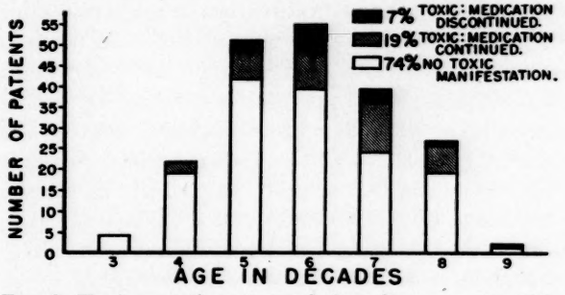

FIG. 2. Toxic manifestations of phenylbutazone in 200 patients with gout.

among these patients with gout. In previous communications[6] we have reported 0.6 per cent incidence of agranulocytosis among 800 patients. One of the other serious reactions attributed to phenylbutazone, namely, activation of peptic ulcer, has not been encountered among this group of 200 gout patients. In daily studies of uropepsin excretion before, during and after a period of phenylbutazone medication in one patient there was no deviation from the normal. *

In Figure 2 the toxic manifestations of phenylbutazone in gout are distributed among the patients according to their ages in decades. It will be seen that there is no apparent correlation between age and incidence of toxic reaction.[6]

In Figure 3 will be seen a comparison of the toxicity of phenylbutazone in gout and various other diseases. In order to arrive at this comparison the punched cards on 600 patients with various rheumatic diseases were shuffled and 200 selected at random. These were then classified in the same manner as those with gout. It was determined that 19 per cent of the patients with gout showed some clinical toxicity which was not serious enough to warrant discontinuance of medication whereas 23.5 per cent of the other patients showed a similar degree of toxicity. Of greater interest, however, is the fact that while 22 per cent of patients with other diseases discontinued medication due to toxic reaction, only 7 per cent of those receiving phenylbutazone were obliged to discontinue medication because of toxic side effects. The net result is that 74 per cent of the 200 patients with gout showed no toxic side effects as compared with 54.5 per cent of other patients showing no toxicity.

In Table VI a comparison is made of the occurrence of toxic side reactions due to phenylbutazone in the group of patients with acute gout (Stage I) as compared with those with

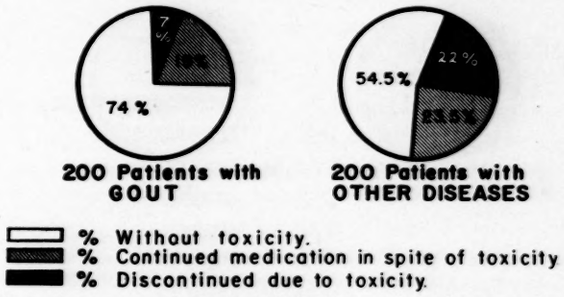

FIG. 3. Comparison of toxicity of phenylbutazone in gout and various other diseases.

chronic gouty arthritis (Stage II). As might be expected, those with intermittent acute exacerbations of gout were generally treated on an interval basis whereas patients with chronic

TABLE VI
COMPARISON OF PHENYLBUTAZONE TOXICITY IN ACUTE AND CHRONIC GOUT

	Acute Gout	Chronic Gouty Arthritis	Combined Total
Without toxicity	59 (87%)	89 (68%)	148 (74%)
Continued medication in spite of toxicity	6 (9%)	32 (24%)	38 (19%)
Discontinued due to toxicity	3 (4%)	11 (8%)	14 (7%)
Totals	68 (100%)	132 (100%)	200 (100%)

gouty arthritis were maintained for longer periods than those in the acute group. Consequently the occurrence of toxicity is appreciably higher in chronic patients. Among these the incidence of toxicity of moderate degree was 24 per cent as against 9 per cent in the acute group. The toxicity became severe enough to warrant discontinuance of medication in 8 per cent of the chronic gouty arthritics as compared to only 4 per cent in the acute group.

In studying the duration of phenylbutazone medication in relation to its discontinuance because of side effects, it became apparent that severe side effects usually occurred early in the course of treatment. Among the 200 patients

* Ernestine Hutchins of Dr. Garnett Cheney's laboratory performed these uropepsin studies.

the distribution was as follows: There were 101 patients treated for fifty days or less; in this group ten patients discontinued medication due to toxic reactions. Among twenty patients treated from fifty to ninety-nine days, only three had to discontinue therapy; while in a group of

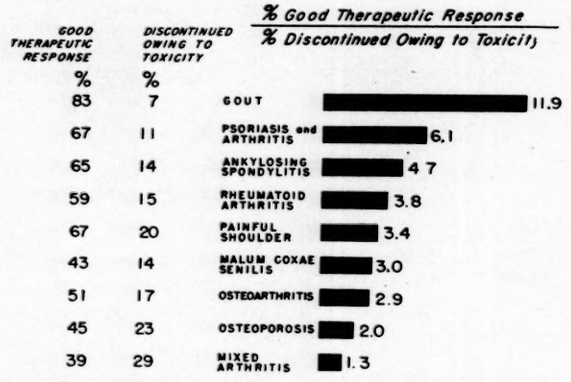

FIG. 4. Clinical usefulness of phenylbutazone.

seventy-nine patients treated for periods from 100 to 800 days, none was obliged to discontinue phenylbutazone due to toxic side effects.

The clinical usefulness of phenylbutazone may roughly be approximated by computation of the ratio of per cent of patients with good therapeutic response (grades I and II) to per cent of patients unable to tolerate the medication.[6] In Figure 4 such ratios are presented demonstrating a quotient of 11.9 for gout as compared with 4.7 for ankylosing spondylitis, 3.8 for rheumatoid arthritis and only 1.3 for mixed arthritis. This comparison emphasizes that phenylbutazone is employed with more advantage in gout than in other painful musculoskeletal disorders.

Mechanism of Action of Phenylbutazone in Gout. Since phenylbutazone appears to exert a specific effect in gout it has been of interest to investigate its mechanism of action. The observation was made early that phenylbutazone administration results in a marked depression in serum uric acid.[3,4,8–10] There has been disagreement, however, among various observers[4,7,10,11] as to whether or not phenylbutazone produces increased urinary excretion of uric acid. In spite of serial determinations in a number of gouty subjects receiving phenylbutazone we have been unable to corroborate the reports of others that phenylbutazone causes increased urinary excretion of uric acid. The discrepancy may be due to the fact that some observers report uric acid excretion in mg. per 100 ml. of urine rather than in gm. per twenty-four hours. Urine volume decreases in many instances for several days after phenylbutazone administration. The total amount of uric acid in a twenty-four-hour period may actually remain constant or be less than prior to treatment while its concentration per 100 ml. of urine may rise. Likewise, it is worthy of note that following the administration of phenylbutazone the serum uric acid tends to decrease in both the gouty and non-gouty individual. It is perhaps worth while to reemphasize at this point, however, that in the maintenance therapy of chronic gouty arthritis the use of small doses (100 mg. daily) of phenylbutazone prevents acute exacerbation of symptoms. At the same time uric acid levels remain unaffected and may even rise to higher levels.

Delfel and Griffin,[12] using P^{32} to study the effect of phenylbutazone on nucleic acid metabolism in the rat, demonstrated that there is increased synthesis of ribonucleic acid and that there appears to be a delay in degradation of the nucleic acids studied. While similar experiments have not yet been performed on a clinical level, the suggested delay in degradation of nucleic acid by phenylbutazone may present the key to the fundamental mechanism of beneficial action in gout.

Further studies to clarify the site of action of phenylbutazone have included assays of enzymes concerned with the metabolism of purines. At the time of this report xanthine oxidase and adenosine deaminase have been investigated in homogenates of rat liver and intestine. These enzymes have been found to be unaffected by the administration of phenylbutazone.[13] Currently, nucleoside phosphorylase is being investigated. Obviously, considerable work is yet to be done to elucidate the precise mechanism of action of phenylbutazone.

Phenylbutazone in a concentration of 1:5000 will completely inhibit the growth of yeast.[14] This property of phenylbutazone has served as a tool for investigating compounds which might possibly interfere with its action. In a series of determinations, glucose, ascorbic acid, glutathione, cysteine, dimercaptopropanol, folic acid, citrovorum factor, xanthine oxidase, thiamine hydrochloride, glycine, adenosine-5-monophosphate, vitamin B_{12}, B-complex, glutamic acid, ammonium chloride, pyridoxine and niacinamide have been tested and do not prevent the inhibitory action of phenylbutazone on yeast growth. On the other hand, the addition of sodium bicarbonate in a concentration of 1:1000 lessened by 70 per cent the inhibitory

effect of phenylbutazone on the growth of yeast. This partial reversal of inhibition was accomplished in a buffered medium without change in the hydrogen ion concentration.

SUMMARY

1. The therapeutic efficacy of phenylbutazone was evaluated in 200 patients with acute gout or chronic gouty arthritis. Major improvement or complete remission was achieved in 84 per cent of these patients. Males responded more favorably than did females. Acute gout was more amenable to phenylbutazone therapy than was chronic gouty arthritis.

2. Among 408 patients with painful musculoskeletal disorders other than gout, the beneficial effect of phenylbutazone was appreciably less in those patients who had elevated serum uric acid than in those with normal uric acid levels. This suggests that the characteristic diminution of serum uric acid promoted by phenylbutazone may not be the most important pharmacologic action of the drug.

3. It is our impression that intramuscular administration effects a more rapid remission of acute gout than does oral phenylbutazone.

4. Maintenance therapy in chronic gouty arthritis with phenylbutazone, 100 to 600 mg. daily, greatly reduced the attack rate, severity and duration of acute exacerbations. This control was exerted even in the presence of serum uric acid levels which had again risen to pretreatment magnitude. In no case were tophi observed to increase or decrease in size.

5. Seventy-one toxic side effects occurred in fifty-two (26 per cent) of the 200 gouty patients. In fourteen patients (7 per cent) toxicity was severe enough to warrant discontinuance of the drug. The most common untoward actions were edema and nausea. There was no case of agranulocytosis or activation of peptic ulcer among these patients. The age of the patient did not appear to influence the incidence of toxicity. Undesirable effects were less severe in gout than in other painful musculoskeletal disorders and usually occurred early in the course of treatment.

6. In homogenates of rat liver and intestine, phenylbutazone did not inactivate xanthine oxidase or adenosine deaminase. The drug was found to inhibit the growth of yeast.

Acknowledgment: In the course of this thirty-month study the combined efforts of many people contributed greatly to its successful termination. We wish to thank Dr. Albert Hemming of Geigy Pharmaceuticals, New York, for his helpful advice during the course of the study and Geigy Pharmaceuticals for grants in aid. We express our thanks to Dr. Windsor C. Cutting, Professor of Pharmacology and Therapeutics for his advice and counsel. Dr. Lincoln E. Moses of the Department of Statistics kindly helped us in the statistical treatment of the data. Esther Larson and Margaret Davis made most of the numerous laboratory tests necessary for the clinical control of the patients.

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The Effect of Intravenous Colchicine on Acute Gout*

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In the past the parenteral treatment of gout with colchicine consisted of the intravenous injection of the contents of a 20 cc. ampule containing 0.65 mg. of colchicine, 1 gm. of sodium iodide and 1 gm. of sodium salicylate. Six years ago one of our patients, C. S., was injected intravenously with this preparation for relief of an acute attack of gout and a severe intestinal hemorrhage resulted. Similar side effects have been seen by another observer.[1]

TABLE I

EFFECTS OF INTRAVENOUS INJECTION OF COLCHICINE IN SIXTEEN GOUTY SUBJECTS

Name	Sex	Age	Known Duration of Gout (yr.)	Uric Acid mg. % Blood (Whole Blood)	Colchicine Intravenously				Side Effects	Therapeutic Response	Remarks
					1/100 gr. in 1 cc.		1/100 gr. in 2 cc.				
					No. Injections	Period	No. Injections	Period			
W. W.	M	31	4	6.9	2	2 days	3	4 days	None	Good	.....
R. R.	M	50	10	6.2	5 2 3	1 weekly 2 days 5 days	2	2 days	None	Good	.....
M. H.	M	75	15	4.7	2	1 weekly	..	.....	None	Good	.....
F. L.	M	57	18	7.9	2	2 days	..	.....	None	Good	.....
B. B.	M	52	11	6.8	2 3	2 days 3 days	..	.....	None	Good	.....
P. C.	M	40	5	4.0	3	3 days	8	2 weeks	None	Fair	With last dose, given cortisone 200 mg. for a day; response better than with colchicine alone
C. S.	M	50	8	8.0	3	3 days	2	2 days	None	Good	Cortisone made his symptoms worse
A. W.	M	60	5	7.0	..	.....	1	1 day	None	Good	.....
W. L.	M	78	9	11.5	..	.....	2	2 days	None	Good	.....
H. B.	M	71	10	5.0	..	.....	1	1 day	None	Good	.....
J. D.	M	50	2	5.0	..	.....	3	3 days	None	Good	.....
F. H.	M	55	20	5.6	2	2 days	..	.....	None	Good	.....
J. S.	M	59	1	6.9	..	.....	1	1 day	None	Good	.....
A. P.	M	59	6	7.3	..	.....	2	2 days	None	Good	.....
W. C.	M	62	1	5.3	..	.....	1	1 day	None	Good	.....
H. G.	M	51	2	5.0	..	.....	3	3 days	None	Good	.....

Since it was thought that some of the side effects might be due to salicylate or iodide sensitivity, a modification† of the standard form was pre-

† Supplied by Dr. Rice of Eli Lilly Company.

* From the Arthritis Clinic, St. Luke's Hospital, New York, N.Y.

pared containing 0.65 mg. (1/100th grain) of colchicine in distilled water in 1 cc. and 2 cc. ampules. Such a formulation would have the following advantages: (1) No danger of salicylate sensitivity; (2) no danger of iodide sensitivity; (3) no additional load of sodium to patients who have gout and possible cardiac decompensation; (4) less chance of gastrointestinal upset; and (5) less chance of a local slough, if solution is spilt outside of vein.

This modified preparation was administered to sixteen patients suffering from acute attacks of gout, diagnosed by character of attacks, history, x-ray studies, uric acid levels in whole blood (serum is preferred) and most important by the immediate response to the intravenous injection of colchicine in each instance. (Table I.)

In some cases up to eight injections were required to bring an attack under complete control. In four cases one injection aborted the attack. Pain and swelling often begin to subside within five to fifteen minutes following the intravenous injection.

For those who are prone to attacks of gout the intravenous injection of colchicine is recommended.

SUMMARY

Colchicine in a solution without added salicylate or iodide was administered intravenously to sixteen patients. A rapid response was noted in most instances.

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Comparative Renal Responses to Water and the Antidiuretic Hormone in Diabetes Insipidus and in Chronic Renal Disease*

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THE "facultative" reabsorption of water, occurring presumably in the renal distal tubule, is believed to be controlled by the antidiuretic hormone (ADH) originating in the neurohypophysis.[1] A deficiency of the hormone diminishes this facultative reabsorption of water and causes diabetes insipidus, a syndrome characterized by polyuria, polydipsia and the excretion of urine of low specific gravity.[2]

Reabsorption of water in the distal tubule may be impaired, however, not only because of a deficiency of the antidiuretic hormone but because the end-organ, the tubular cell, is unable to respond normally to circulating ADH. Thus there have been several reports[3–6] dealing with "nephrogenic" or "congenital" diabetes insipidus, a condition caused by an apparently inborn defect in renal tubular metabolism. As a result of this tubular cell defect there is diminished reabsorption of water in the distal segment of the nephron, which is unresponsive to extracts of the posterior lobe of the pituitary. Such patients exhibit polyuria, with consequent dehydration and polydipsia.

Tubular dysfunction occurs also in some patients with (chronic) renal disease, as indicated by polyuria and inability to excrete concentrated urine.[7] It may then be postulated that in these patients the tubular cell, the end-organ, is unable to respond normally to circulating ADH, and one might consequently expect to observe physiologic phenomena similar to those associated with diabetes insipidus caused by a deficiency of the antidiuretic hormone.

The present study was designed to investigate this postulate by measuring water diuresis and antidiuresis in patients suffering from diabetes insipidus and from chronic renal disease. The specific aims were: (1) to study the renal excretion of water and electrolytes in these two groups of subjects during (*a*) periods of diminished secretion of (endogenous) antidiuretic hormone, ADH, under conditions of oral or intravenous hydration, (*b*) periods of increased secretion of ADH in response to dehydration and (*c*) twenty-four-hour collection periods; and (2) to observe the effects of exogenous ADH (pitressin®) on the renal excretion of water and electrolytes.

EXPERIMENTAL

Four patients with diabetes insipidus on a standard hospital diet and five with chronic renal disease on a diet containing 200 mg. Na per day served as subjects for these studies. All patients were permitted water ad libitum except during experimental periods. Of the four patients with diabetes insipidus three had the syndrome secondary to invasion of the posterior pituitary by metastatic neoplasm, while the fourth suffered from Hand-Schüller-Christian disease. In four of the patients with renal disease the diagnosis was chronic glomerulonephritis, the fifth had chronic pyelonephritis. More detailed clinical information concerning these subjects is presented in the Case Summaries.

The responses of the four patients with diabetes insipidus to single intravenous doses of pitressin were studied. Each subject was in a fasting state for fifteen hours. Prior to the beginning of the experiment one glass of water was taken every half-hour for two hours. An infusion of 5 per cent glucose in water (average flow of

* From the Department of Medicine, The Mount Sinai Hospital, New York City. This work was aided in part by a grant from the American Heart Association and by a United States Public Health Service Research Grant (H-1245.) An abstract of this work appeared recently; WHITE, A. G., KURTZ, M. and RUBIN, G. Impaired renal response to the antidiuretic hormone in chronic renal disease. *J. Clin. Investigation*, 32: 611, 1953.

† Stanley D. Kops Memorial Fellow in Medicine.

10 cc. per minute) was then started and continued throughout the experiment. When the rate of urine flow reached a plateau, 0.57 mU./kg. of pitressin was injected rapidly into the infusion tubing near the needle. Endogenous creatinine clearances were measured throughout each experiment.

The urinary bladder was washed out with distilled water and air at the end of each collection period (10 to 15 minutes each) through an indwelling six-holed catheter. Blood specimens were obtained at the beginning of an experiment, at the height of diuresis, at the height of antidiuresis and at the end of the procedure.

The calculations and definitions are the same as those we have described previously.[8] The

$$\text{"per cent inhibition"} = \frac{\text{Expected diuresis minus observed diuresis} \times 100}{\text{Expected diuresis}}$$

The "expected diuresis" is the urine flow that would have been obtained if the initial rate, observed when pitressin was injected, had been maintained throughout the period of pitressin effect.

In the five patients with chronic renal disease the glomerular filtration rate (endogenous creatinine clearance and inulin clearance) and the renal plasma flow (para-aminohippurate clearance) were determined.[9] At the end of the third collection period the intravenous administration of 5 per cent glucose in water at 10 cc. per minute was begun; and after the urine flow appeared to be stabilized, intravenous pitressin was administered as described above.

An oral water tolerance test[10,11] was performed in each of the patients with chronic renal disease; 1,500 cc. of water was administered orally during a thirty-minute period to four of these patients; the fifth took 1,000 cc. A concentration test (sixteen hours of dehydration) was performed in each of the renal patients. In some of the patients twenty-four-hour collections of urine were made and the concentrations of sodium, potassium and chloride in the urine and blood were measured.

Hematocrit determinations on heparinized blood were performed by centrifuging in Wintrobe tubes at 2,500 r.p.m. for thirty minutes. Serum and urinary creatinine concentrations were measured by Peters' modification of the Folin method;[12] urinary sodium and potassium and serum potassium with an internal standard flame photometer;[13] chloride by the Van Slyke-Hiller modification of Sendroy's iodometric method;[14] and urinary glucose by the method of Benedict.[15] Inulin and para-aminohippurate clearances were measured by methods referred to previously.[9]

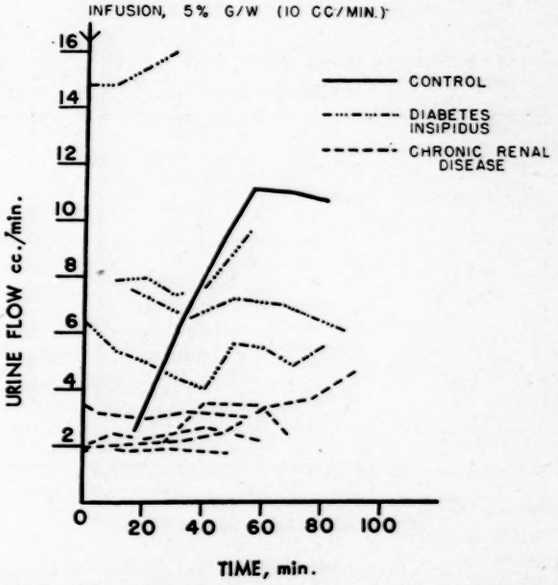

FIG. 1. The effect of intravenous hydration with 5 per cent glucose in water (infused at 10 cc./min.) on urine flow. The curve for a control subject is presented for comparison.

RESULTS

Excretion of Water. Water Diuresis: As has been demonstrated previously,[8] following the onset of intravenous hydration with 5 per cent glucose in water (infused at 10 cc./min.) the normal subject excretes urine at a rate that rises to a peak at 85 ± 32 minutes. (Fig. 1.) In contrast, the curve of urine flow (cc./min.) in the patients with renal disease is almost flat during the first forty minutes, and in three of the patients with diabetes insipidus the slope actually appears to be negative during this period.

Table 1 indicates the per cent of the filtered water load excreted in the urine; "minimal" (occurring usually at the onset of the intravenous infusion) and "maximal" values for the period of intravenous hydration are presented. The average paired difference ("maximal" minus "minimal") was 6.7 per cent for the patients suffering from renal disease, 2.4 per cent for those with diabetes insipidus and 11.5 per cent for the control subjects.

Figure 2 demonstrates impaired water diuresis

following oral ingestion of 1,500 cc. water by the patients with renal disease. The curves of urine flow are relatively flat and do not show the sharp peak occurring normally between 90 and 120 minutes. In four hours patients Y. S., J. W., W. D., G. F. and S. S. excreted 37, 48, 36, 44 and 46 per cent, respectively, of the ingested oral water load.

Table II shows that during the oral water tolerance test in these subjects the mean urinary specific gravity was 1.009 initially, decreased to 1.002 at the height of water diuresis and reached 1.003 at the end of the test period.

Twenty-four-Hour Renal Excretion of Water. Table III shows the per cent of the filtered water load represented by the volumes of urine excreted by two of the patients with renal disease and one with diabetes insipidus. For the renal subjects, J. W. and Y. S., this was 8.1 and 8.4 per cent, respectively, while case A. K. with diabetes insipidus excreted 4.9 per cent of his daily filtered water load.

TABLE I

RENAL HEMODYNAMICS AND PER CENT OF FILTERED WATER LOAD EXCRETED DURING INTRAVENOUS HYDRATION WITH 5 PER CENT GLUCOSE IN WATER (10 CC./MIN.)

Patient	Inulin				Creatinine					Clearance Ratio	PAH
	Clearance (cc./min.)	Per cent of Filtered Water Load Excreted			Serum Conc'n. (mg./100 cc.)	Clearance (cc./min.)	Per cent of Filtered Water Load Excreted			C_{Cr}/C_{In} (Max.)	Clearance (cc./min.)
		Min.	Max.				Min.	Max.			
Chronic Renal Disease		(1)	(2)	(2)–(1)			(1)	(2)	(2)–(1)		
S. S.	8.0	23.0	32.4	9.4	6.3	6.4	28.8	40.5	11.7	1.25	.....
G. F.	19.1	15.4	16.8	1.4	2.9	18.7	15.8	17.2	1.4	1.02	73
W. D.	13.1	13.2	14.3	1.1	10.8	10.9	15.9	17.2	1.3	1.20	21
J. W.	23.7	7.9	20.2	12.3	3.3	33.0	5.7	14.5	8.8	0.72	193
Y. S.	13.5	15.4	25.8	10.4	4.3	13.9	14.8	25.1	10.3	0.97	35
Mean	15.5	15.0	21.9	7.0	5.5	16.6	16.2	22.9	6.7	1.03	80.6
Diabetes Insipidus											
A. K.	....	....	....	....	0.86	142.0	4.3	5.3	1.0	....	.....
A. F.	....	....	....	....	1.51	57.0	12.8	16.8	4.0	....	.....
F. R.	....	....	....	....	1.84	70.0	5.6	9.0	3.4	....	.....
P. V.	....	....	....	....	1.77	37.5	39.4	40.6	1.2	....	.....
Mean	....	....	....	....	1.5	76.6	15.5	17.9	2.4	....	.....
Controls*											
M. I.	....	....	....	....	0.94	57.0	2.0	19.5	17.5	....	.....
J. P.	....	....	....	....	0.90	83.0	3.1	13.4	10.3	....	.....
D. S.	....	....	....	....	0.89	67.0	8.5	21.0	12.5	....	....
S. G.	....	....	....	....	0.90	103.0	2.1	14.5	12.4	....	.....
E. N.	....	....	....	....	0.82	122.0	1.2	12.0	10.8	....	.....
E. B.	....	....	....	....	0.65	67.0	4.9	10.2	5.3	....	.....
Mean	....	....	....	....	0.85	83.0	3.6	15.1	11.5	....	.....

*Reported previously by White, Rubin and Leiter (1951).

Pitressin Antidiuresis. Table IV and Figures 3 and 4 indicate the effect of intravenous pitressin (0.57 mU./kg.) on the urinary excretion of water in the patients studied. The average duration of pitressin antidiuresis was 36.8 ± 11.1 minutes for the patients with renal disease and 36.0 ±5.8 minutes for those with diabetes insipidus. The mean "per cent inhibition" was 13.0 ± 13.6 for the patients suffering from chronic renal disease while it averaged 29.0 ± 19.0 in those with diabetes insipidus. Under the same experimental conditions, the mean period of pitressin antidiuresis in control subjects was 63.8 ± 9.2 minutes while the "per cent inhibition" averaged 55.6 ± 5.6 per cent.

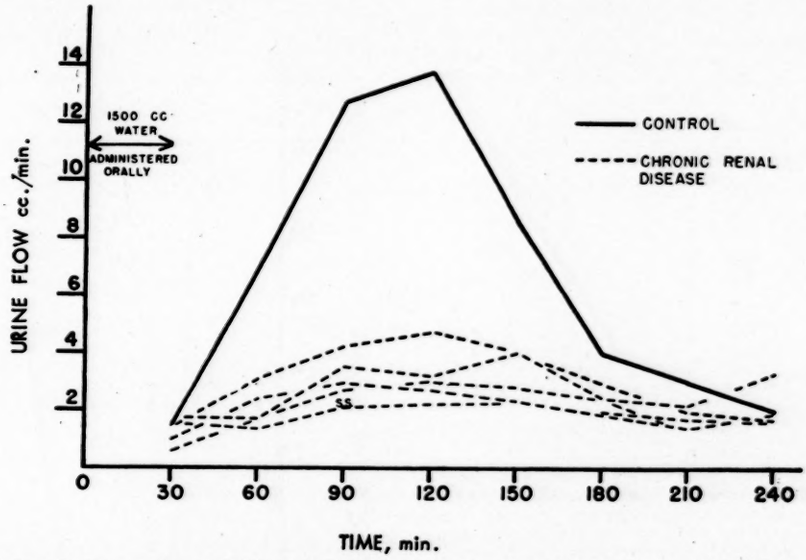

FIG. 2. Water diuresis following the oral ingestion of 1,500 cc. water within thirty minutes by patients with chronic renal disease.

TABLE II

SPECIFIC GRAVITY OF THE URINE DURING AN ORAL WATER TOLERANCE TEST IN CHRONIC RENAL DISEASE

Patient	Initial	"Peak" Diuresis	Final (300 min.)
S. S.	1.010	1.004	1.002
G. F.	1.008	1.002	1.001
W. D.	1.010	1.002	1.006
J. W.	1.006	1.001	1.002
Y. S.	1.010	1.003	1.003*
Mean	1.009	1.002	1.003

* At 180 min.

Serum Electrolytes (*Na*, *Cl*, *K*). The patients with renal disease, as well as those with diabetes insipidus, showed no significantly abnormal "initial" concentrations of sodium, chloride or potassium in the serum. (Table V.) Neither intravenous hydration with 5 per cent glucose in water nor the intravenous administration of pitressin (0.57 mU./kg.) had any significant effect on the serum electrolytes of the patients with diabetes insipidus. It will be noted that in each of three patients with renal disease, Y. S., W. D. and J. W., the concentration of serum sodium at the height of antidiuresis was significantly lower than the corresponding initial value.

TABLE III

PER CENT OF THE TWENTY-FOUR HOUR FILTERED WATER LOAD EXCRETED IN THE URINE IN RENAL DISEASE AND IN DIABETES INSIPIDUS

Patient	(1) Urine Vol. (cc./24 hr.)	(2) Filtered* H_2O Load (cc./24 hr.)	$\frac{(1)}{(2)} \times 100$
Renal Disease:			
J. W.	2970	37,440	8.1
Y. S.	2490	29,232	8.4
Diabetes Insipidus			
A. K.	6080	123,840	4.9

* Endogenous creatinine clearance.

TABLE IV

EFFECT ON URINE FLOW OF A SINGLE INTRAVENOUS DOSE (0.57 MU./KG) OF PITRESSIN ADMINISTERED DURING CONTINUOUS INTRAVENOUS HYDRATION WITH 5 PER CENT GLUCOSE IN WATER (10 CC./MIN.)

Patient	Hydration	Antidiuresis		
	Pre-pitressin Urine Flow* (cc./min.)	Duration Pitressin Effect (min.)	Per cent Inhibition	Peak Antidiuresis† (cc./min.)
Chronic Renal Disease				
S. S.	2.6	36	5.4	1.9
W. D.	2.8	30	6.5	1.5
G. F.	3.7	49	24.2	1.4
J. W.	4.1	46	31.8	2.5
Y. S.	3.3	0	0	...
Mean ± S.D.	3.3 ± 0.6	37 ± 11	13 ± 13.6	1.7 ± 0.5
Diabetes Insipidus:				
A. K.	7.5	42	44.6	0.0
A. F.	7.8	36	27.0	4.3
F. R.	5.3	29	3.0	2.9
P. V.	14.8	38	41.5	3.9
Mean ± S.D.	8.9 ± 4.1	36 ± 5.8	29.0 ± 19	11.1 ± 1.9
Mean ± S.D. for seven *controls*‡	12.1 ± 2.8	64 ± 9	54.3 ± 5.4	1.1 ± 0.6

* Pre-pitressin urine flow signifies the rate of urine flow at the time of pitressin administration. This represents the rate usually maintained at a plateau for at least two or three collection periods.

† Peak antidiuresis denotes the minimum rate of urine flow during a ten-minute collection period following the intravenous injection of pitressin. Compare with Figures 3 and 4.

‡ Reported previously by White, Rubin and Leiter (1951).

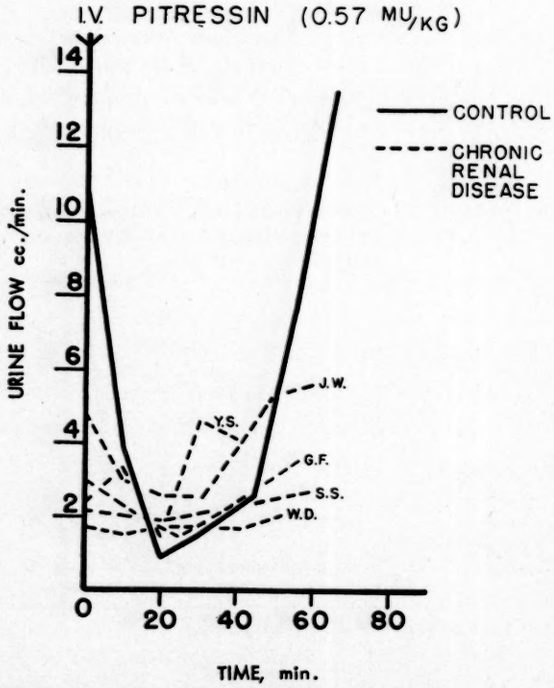

FIG. 3. The effect of intravenous pitressin (0.57 mU./kg.) on the urine flow in continuously hydrated (intravenous 5 per cent glucose in water at 10 cc./min.) patients suffering from chronic renal disease.

Urinary Electrolytes (*Na, Cl, K*). As shown in Table VI, pitressin had no significant effect on the urinary excretion of Na, Cl or K (mEq./min.).

Renal Clearance Studies. The studies on renal hemodynamics measured by means of "clearances" of endogenous creatinine, inulin or para-

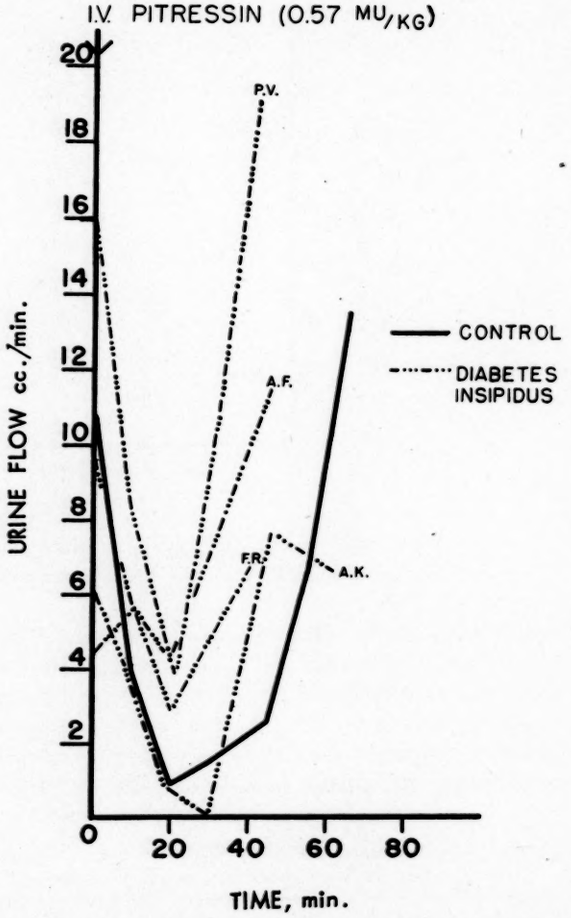

FIG. 4. The effect of intravenous pitressin (0.57 mU./kg.) on the urine flow in continuously hydrated (intravenous 5 per cent glucose in water at 10 cc./min.) patients suffering from diabetes insipidus.

aminohippurate are presented in Table I. The creatinine clearance averaged 16.6 ± 10.2 cc./min. in the patients with renal disease and 76.7 ± 45.3 cc./min. in the patients suffering from diabetes insipidus. In the renal patients the inulin clearance averaged 15.5 ± 6.0 cc./min. (range: 8.0 to 23.7) while that of PAH averaged 80.5 ± 78.0 cc./min. (range: 21.0 to 193.0). In the patients with renal disease the average of the endogenous creatinine/inulin clearance ratios was 1.03 (ranges: 0.72 to 1.25).

COMMENTS

Excretion of Water. Water diuresis: Following intravenous hydration in the patients with diabetes insipidus the curve of urine flow was essentially flat, not showing the gradual rise to a peak at approximately eighty-five minutes characteristic of the normal subject. Such "blunting" of the diuresis curve has been reported previously in human cases of diabetes insipidus[16] as well as in rats[17] with the syndrome induced experimentally.

The onset of diuresis and the attainment of a peak flow following hydration of the normal subject has been attributed to "inactivation" of endogenous circulating antidiuretic hormone,[1] thus inhibiting the facultative reabsorption of water in the renal distal tubule. As a result, up to approximately 15 per cent of the filtered water load may become available for excretion in the urine. When the facultative reabsorption of water is released from control by the antidiuretic hormone, as in diabetes insipidus, one might anticipate that the onset of hydration would not be followed by a "lag" period preceding the attainment of a peak diuresis but that there would be almost immediate excretion of approximately maximal (for the given experimental conditions) amounts of water. Further support is lent this speculation by referring to Table 1. It will be noted that in the patients with diabetes insipidus there is only a small difference (under the present experimental conditions) between the "minimal" and "maximal" values of 100 P/U (for creatinine). This suggests that these patients were indeed excreting amounts of water near the maximum of their capacity at the beginning of the intravenous infusion.

As already pointed out, the facultative reabsorption of water may also be released from control by ADH because the end-organ, the tubule, is incapable, as a result of intrinsic renal disease, of responding normally to circulating ADH. The curve of water diuresis following the onset of hydration would then resemble that demonstrated for diabetes insipidus. This is what we observed: namely, the almost immediate attainment of a plateau in the rate of urine flow.

Of additional interest are the figures in Table 1 indicating the per cent of filtered water load excreted by the patients with renal disease and those with diabetes insipidus. Although intravenous hydration with 5 per cent glucose in water administered at 10 cc./min. does not normally produce maximal diuresis, the patients with renal disease reached an average excretion of 23.8 per cent of the filtered water load (range: 15.1 to 41.5 per cent), based on measurements of inulin clearance. One of the patients with diabetes insipidus, P. V., reached an excretion of 40.6 per cent of the filtered water load.

Speculative explanations of such a large proportionate excretion of water include: (1) impaired reabsorption of water in the proximal nephron; normally seven-eighths of the filtered

TABLE V

EFFECT OF PITRESSIN ON SERUM ELECTROLYTES

Patient	Initial			Diuresis			Antidiuresis			Final		
	Na (mEq./L.)	Cl (mEq./L.)	K (mEq./L.)	Na (mEq./L.)	Cl (mEq./L.)	K (mEq./L.)	Na (mEq./L.)	Cl (mEq./L.)	K (mEq./L.)	Na (mEq./L.)	Cl (mEq./L.)	K (mEq./L.)
Chronic Renal Disease:												
S. S.	137	103.6	5.0	133	99.7	4.2	126	98.5	4.1	128	97.8	3.9
G. F.	143	100.0	4.4	139	98.9	3.4	...	....	...	....	.....	...
W. D.	135	92.0	4.3	130	92.8	4.0	128	92.8	4.0	....	.....	...
J. W.	136	99.0	5.2	137	99.5	5.3	131	96.5	4.5	....	.....	...
Y. S.	138	102.0	5.6	....	101.8	...	...	.....	...	....	100.4	...
Diabetes Insipidus:												
A. K.	141	100.3	4.0	141	100.3	4.0	141	100.2	4.1	140	100.2	4.0
A. F.	134*	104.1	4.3	137*	101.5	4.9	145	101.0	...	138*	100.0	4.2
F. R.	144	108.9	4.8	138	110.6	4.4	137	111.5	4.5	141	111.5	4.3
P. V	165	119.4	2.7	159	111.0	2.2	158	109.8	2.6	166	119.8	2.6

* Sodium determined gravimetrically.

TABLE VI

URINARY ELECTROLYTE EXCRETION DURING HYDRATION AND PITRESSIN ANTIDIURESIS

Patient	Hydration (H)					Antidiuresis (A)					(H) minus (A)			
	Time (min.)	Urine Flow (cc./min.)	Cl (mEq./min.)	Na (mEq./min.)	K (mEq./min.)	Time (min.)	Urine Flow (cc./min.)	Cl (mEq./min.)	Na (mEq./min.)	K (mEq./min.)	Urine Flow (cc./min.)	Cl (mEq./min.)	Na (mEq/.min.)	K (mEq./min.)
Chronic Renal Disease:														
S. S.	36	2.4	.094	.074	.060	36	2.1	.100	.087	.055	+0.3	−.006	−.013	+.005
G. F.	49	3.1	.011	.031	.032	49	2.1	.017	.038	.028	+1.0	−.006	−.007	+.004
W. D.	30	1.8	.054	.061	.049	30	1.6	.044	.042	.047	+0.2	+.010	+.019	+.002
J. W.	46	4.4	.035	.039	.043	46	3.3	.060	.055	.048	+1.1	−.025	−.016	−.005
Y. S.	23	3.0	.037	.042	.057	..	...	....	....	....	.....	.....	.....	.....
Diabetes Insipidus														
A. K.	42	6.6	.038	.065	.014	42	3.3	.028	.047	.011	+3.2	+.010	+.018	+.003
A. F.	36	8.4	.066	.074	.036	36	6.9	.099	.099	.058	+1.5	−.033	−.029	−.022
F. R.	29	4.4	.274	.272	.058	29	4.4	.294	.293	.064	0	−.020	−.021	−.006
P. V.	38	15.3	.112	.078	.073	38	9.4	.226	.136	.099	+5.9	−.114	−.058	−.026

water load is believed to be reabsorbed in the proximal portion of the tubule and in some of the renal patients (as well as in P. V. who had diabetes insipidus) this amount may well have been diminished. (2) Tubular secretion of water. Recently the hypothesis has been advanced that the renal mechanism for the production of the dilute urine characteristic of diabetes insipidus and of water diuresis is the secretion of water by the distal tubule.[18] Platt[19] has suggested that tubular secretion of water occurs in chronic renal failure. (3) Nickel and his associates[20] have reported recently on renal function and electrolyte excretion in patients with chronic renal insufficiency before and after sodium deprivation. They found that tubular "reabsorption is greatly reduced permitting the escape of a much larger percentage of the filtered water and electrolytes than in the normal" and they conclude that "thus, the factor of osmotic diuresis seems a more likely cause for high values V/C_{in} [percentage of filtered water excreted] than the secretion of water by the tubules."

2. *24-Hour Renal Excretion of Water.* Reference to Table III indicates that although the twenty-four-hour urinary volume may be smaller in renal disease than in diabetes insipidus, when the urinary output is related to the simultaneously filtered water load, the renal patient may actually be excreting a greater fraction of the glomerular filtrate than the patient with diabetes insipidus. Similar calculations of the per cent of the filtered water load excreted during intravenous hydration (Table I) indicate that here, too, the renal patients excreted a higher fraction of the filtered water load than did those with diabetes insipidus.

Pitressin Antidiuresis. The duration of pitressin antidiuresis was shortened equally for the patients suffering from diabetes insipidus and for those with chronic renal disease, but the "per cent inhibition" of diuresis was smaller in the renal group. There are several possible explanations as to why intravenous pitressin may produce subnormal antidiuresis in patients with diabetes insipidus:

1. In normal human subjects all of the endogenous antidiuretic hormone may not be "inactivated"* as a result of intravenous hydration (5 per cent glucose in water flowing at approximately 10 cc./min.). Thus when exogenous pitressin is injected it may have an additive effect along with that of the circulating endogenous antidiuretic hormone that remains, whereas in patients with diabetes insipidus the exogenous hormone (pitressin) acts alone. To test this possibility we performed the following experiment: A normal human subject was hydrated with 5 per cent glucose in water administered intravenously at a rate of 10 cc./min. When the urine flow reached a plateau, the rate of the intravenous infusion was doubled suddenly. If all of the endogenous antidiuretic hormone had been "inactivated" by the smaller infusion rate (10 cc./min.), the subject should have, like a patient with diabetes insipidus, promptly attained a new plateau of urine flow when the infusion rate was doubled to 20 cc./min. This did not occur. Instead there was a gradual onset of a new peak level of diuresis. This suggests that all of the endogenous antidiuretic hormone probably was not "inactivated" during the first portion of the experiment when the infusion rate was 10 cc./min.

2. In diabetes insipidus the renal tubules may be altered functionally by the continued absence of the antidiuretic hormone so that they cannot reabsorb water maximally in response to the rapid, intravenous administration of pitressin in physiologic dosage.

In the present studies the patients with renal disease demonstrated subnormal responses to small doses of intravenous pitressin, and also responded subnormally to endogenous ADH as evidenced by the low urinary specific gravity following dehydration. The exact physiologic or biochemical mechanisms involved in this diminished tubular responsiveness to the antidiuretic hormone cannot now be precisely defined. Several mechanisms may be postulated. The most obvious one is that the distal tubular cell, as a result of disease, cannot respond normally to the antidiuretic hormone. At times the tubular "lesion" might even represent a loss of kidney mass, as demonstrated in the experiments of Hayman and his associates who reported that partial nephrectomy in dogs can cause hyposthenuria. Another possible explanation for the subnormal antidiuretic response to pitressin in the patients with renal disease is that the load of water presented to the distal tubule is so great (as a result of impaired reabsorption in the proximal tubule) that the action of the anti-

* "Inactivated" is used here to define the disappearance of the hormone from the circulating blood, whether resulting from a decreased secretion by the posterior pituitary, detoxification or excretion from the body or a combination of all three processes.

diuretic hormone is masked by the proximal diuresis. It is possible that both mechanisms operate, in some cases probably simultaneously.

Electrolytes (Na, Cl, K). In three of the patients with renal disease, Y. S., W. D. and J. W., intravenous pitressin (0.57 mU./kg.) tended to lower the concentration of sodium in the serum. We have observed a similar phenomenon in patients with cirrhosis of the liver.[8] In accordance with our earlier observations in normal subjects and in hepatic and cardiac patients,[8,21] pitressin (0.57 mU./kg.) had no effect on the urinary excretion of Na, Cl or K (mEq./min.) in the patients with renal disease or diabetes insipidus.

None of the renal patients presented any evidence of salt-losing nephritis during their hospital stay, even after being placed on a diet containing 200 mg. sodium per day.

Renal Clearance Studies. The average of the endogenous creatinine/inulin clearance ratios in this group was 1.03 (range: 0.72 to 1.25). This is a somewhat closer correlation between the two clearances than found by Miller and his associates who have recently summarized the literature on the reliability of the endogenous creatinine clearance as a measure of glomerular filtration rate in renal disease.[22] The measurements of endogenous creatinine clearance in the patients with diabetes insipidus showed a marked variation (37.5 to 142.0 cc./min.). Possible explanations for the lower glomerular filtration rates include: (1) dehydration, (2) malnutrition, (3) hypofunction of a damaged anterior lobe of the pituitary gland or (4) intrinsic renal disease (although no evidence is available to support this latter possibility). Nevertheless, the renal responses to hydration and to pitressin are quite consistent for the entire group despite the variation in glomerular filtration rate.

CASE SUMMARIES

Chronic Renal Disease

S. S., M. S. H. No. 642362, was a fifteen year old white girl who developed hematuria at the age of six following an episode of pneumonia. Proteinuria and occasional hematuria continued up to the time of admission. The patient entered the hospital because of tetany. Laboratory data: blood urea nitrogen, 108 mg. per cent; creatinine, 6.4 mg. per cent; CO_2, 36 vol. per cent; Ca, 4 mg. per cent; P, 17 mg. per cent; Urine examination: 3–4+ albumin, red blood cells, white blood cells, casts. Diagnosis: chronic glomerulonephritis.

G. F., M. S. H. No. 644369, a twenty-nine year old white woman, was well until six years before admission. At this time, while pregnant, she developed the first of many bouts of fever, dysuria and pyuria. Laboratory data: blood urea nitrogen, 43 mg. per cent; creatinine, 3.6 mg. per cent; Urine examination: albumin to 2+, varying amounts of white blood cells and red blood cells with clumps of leucocytes; urine culture yielded enterococcus. Diagnosis: chronic pyelonephritis.

W. D., M. S. H. No. 645184, was a fifty-two year old male Negro with hypertension for twelve years and dyspnea for two years. He entered the hospital because of failing vision for one month. Examination revealed blood pressure 260/215, marked hypertensive retinopathy and a slightly enlarged heart. Blood urea nitrogen, 68–95 mg. per cent; uric acid, up to 9.6 mg. per cent; creatinine, up to 9.3 mg. per cent. Urine examination: albumin 3+, occasional red blood cells and white blood cells, casts. The patient's blood pressure fell on bed rest and low salt diet. He was discharged symptomatically improved but returned several months later in terminal uremia. Autopsy examination revealed chronic glomerulonephritis.

J. W., M. S. H. No. 646296, a thirty-two year old white male, contracted an upper respiratory infection for which he received two injections of penicillin one month before admission. Following the injections, generalized edema and a skin rash occurred. He was admitted to the Hospital because of persistence of these findings. Urine examination on admission: albumin 2+, many red blood cells, white blood cells and casts. Blood urea nitrogen, 36 mg. per cent; creatinine, 4.1 mg. per cent; uric acid, 8.8 mg. per cent. The patient improved symptomatically on prolonged bed rest but the blood urea was increased at the time of discharge. Diagnosis: Chronic glomerulonephritis.

Y. S., M. S. H. No. 646469, a thirty-four year old Japanese male, was found to have proteinura and hypertension during an insurance examination fourteen years before admission. Following an upper respiratory infection five weeks before admission the patient developed dependent edema and facial edema, with marked dyspnea on exertion and cough productive of clear, non-bloody sputum. Laboratory data: blood urea nitrogen, 53–80 mg. per cent; CO_2, 46.5–61.8 vol. per cent; uric acid, 14.1–8 mg.

per cent; creatinine, 7.6–4.1 mg. per cent. Urine examination: albumin 3+, occasional red blood cells, 10–12 white blood cells, and 1–2 casts per high power field. Diagnosis: Chronic glomerulonephritis.

Diabetes Insipidus

A. K., M. S. H. No. 632099, was a twenty year old white male with severe thirst and polyuria for six months (daily fluid intake and output estimated at 14 quarts/day during this period), bone destruction and reabsorption in the region of the upper left first and second molars as well as the lower central incisors one and one-half years prior to admission. Skull x-ray showed well demarcated defect on right side of the occipital bone. Biopsy of left upper maxilla taken in the area of bone destruction showed granulation tissue, histiocytes and eosinophils but no foam cells; specimen considered pathologically to be compatible with a diagnosis of xanthomatous disease. Intravenous hypertonic (2.5 per cent) saline solution, 0.25 cc./kg./min., for forty-five minutes produced no antidiuresis.

A. F., M. H. No. 52669,* a forty-four year old white female, entered the Hospital in November, 1950, with marked increase in fluid intake and output (about 7 L./24 hr.). She had undergone a left radical mastectomy in 1944 and was well until February, 1950, when metastasis to the right lung was observed. By August, 1950, there was evidence of osseous metastases and of cerebral involvement as demonstrated by bilateral papilledema and retinal hemorrhages, as well as by a right occipital palpable mass. Skull x-rays showed metastasis in the region of the sella turcica with considerable erosion of the sella and almost complete disappearance of the landmarks. Dehydration overnight yielded urine with a maximum specific gravity of 1.002.

F. R., M. S. H. No. 638628, a fifty-six year old male, was well until five months prior to hospital admission, at which time he noted the insidious onset of thirst associated with increased intake and output of water. He drank up to 7 quarts of water per day, reduced to approximately 5 quarts when given various posterior pituitary preparations. Intermittent headaches occurred three months after the onset of his present illness. Physical examination was essentially normal except for very mild elevation of systolic blood pressure (150–176, with a diastolic pressure of 90). Neurologic examination was entirely normal except for a lumbar puncture which revealed an initial pressure of the spinal fluid of 300 mm. with the final pressure 120 mm. after 10 cc. were withdrawn. Skull x-rays were normal as were an electroencephelogram and visual field determinations. Glucose tolerance curve was slightly diabetic although no glucose appeared in any of the urine specimens during the test. There was no azotemia. A sixteen-hour fluid deprivation test was performed during which 4,000 cc. of urine (maximum specific gravity of 1.010) were voided, with a 7 pound weight loss.

P. V., M. S. H. No. 715, a fifty-eight year old white male, entered with a six-week history of polyuria and polydipsia. Urine output ranged from 10 to 17½ L. per day. Intravenous hypertonic 2.5 per cent saline yielded no antidiuresis. Dehydration overnight resulted in the excretion of urine with a specific gravity of 1.000. Postmortem examination revealed carcinoma of the lung with metastases to the posterior pituitary gland.

SUMMARY AND CONCLUSIONS

1. Four patients with diabetes insipidus and five with chronic renal disease were studied to investigate what seemed to be a similar impairment in the "facultative" reabsorption of water in these two disease states.

2. Following oral hydration (1,500 cc. within thirty minutes) the patients with renal disease showed impairment of water diuresis, as demonstrated by lack of attainment of a normal peak diuresis and excretion of a subnormal quantity of water during the five-hour period of observation.

3. During intravenous hydration with 5 per cent glucose in water at 10 cc./min. both groups of patients showed prompt attainment of a plateau of urine flow, in contrast to the normal curve which reaches a peak at approximately eighty-five minutes under the same experimental conditions. Suggestions are made concerning the possible physiologic significance of these findings.

The patients with renal disease tended to excrete an even higher proportion of the filtered water load than did those with diabetes insipidus. The twenty-four hour volume of urine was not as large in the patients with chronic renal disease, however, because of their greatly diminished glomerular filtration rate.

* A. F. was a private patient of Dr. Daniel Laszlo at Montefiore Hospital, to whom the authors are indebted for permission to make some measurements and to report on them here.

4. Both groups of patients demonstrated subnormal antidiuresis following the intravenous administration of 0.57 mU./kg. of pitressin during continuous intravenous hydration with 5 per cent glucose in water (10 cc./min.). Possibly responsible physiologic mechanisms are discussed.

5. The only observed disturbance in either serum or urinary electrolytes during the hydration or antidiuresis (pitressin) experiments was a tendency for the concentration of sodium in the serum to decrease following administration of pitressin to patients with renal disease.

6. It is concluded that, because of the apparent impairment of "facultative" reabsorption of water in patients with chronic renal disease, they may be considered to have an "end-organ" defect type of diabetes insipidus, in contrast to the syndrome caused by deficient elaboration of the antidiuretic hormone which may be designated "central" diabetes insipidus. The physiologic mechanisms responsible for the diminished tubular responsiveness to the antidiuretic hormone cannot be defined precisely at this time. In addition to intrinsic damage to the distal tubular cells as a result of renal disease, the load of water presented to the distal tubule may be excessive due to impaired reabsorption of water in the proximal tubule.

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Potentially Reversible Renal Failure Following Excessive Calcium and Alkali Intake in Peptic Ulcer Therapy*

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In the treatment of peptic ulcer the danger of producing systemic alkalosis and renal dysfunction with absorbable alkalies was first pointed out by Hardt and Rivers[1] in 1923 and has been repeatedly noted since that time.[2,3] Cope[4] in his excellent analysis of the problem observed a variable time interval, varying from months to years, between the beginning of treatment and the onset of metabolic disturbances. In 1949 Burnett et al.[5] described six similar cases with metastatic calcification in addition to the alkalosis and renal dysfunction. Two additional cases of this latter type have since been reported.[6,7]

Recently, four patients with renal damage, hypercalcemia and metastatic calcification resulting from excessive calcium and alkali intake have been observed at the New England Center Hospital. In two of these renal function returned virtually to normal after therapy. The following case summaries demonstrate the natural history of this disorder and indicate the need for early diagnosis and treatment.

CASE SUMMARIES

CASE 1. A. B. (N.E.C.H. No. 48-658), a fifty-seven year old male, was admitted March 20, 1950 because of rheumatoid arthritis. There was a history of peptic ulcer, first diagnosed in 1925, and treated almost continuously with milk, sodium bicarbonate and calcium carbonate. During the eight years prior to admission the patient estimated that he had ingested at least 1 quart of milk and 2 gm. of calcium carbonate per day, in addition to his usual diet. Ureterolithiasis had occurred in 1945. During a hospitalization elsewhere, four months before entry, six of ten urinalyses had disclosed minimal traces of albumin but were otherwise normal. In routine urine specimens a maximum specific gravity of 1.025 had been obtained. The nonprotein nitrogen level of the blood had varied between 35 and 44 mg. per 100 cc.

On entry, physical examination revealed pallor and joint changes suggestive of rheumatoid arthritis.

Urine examination disclosed 2+ albuminuria, granular and hyaline casts, rare red and white cells, and hyposthenuria. (Other laboratory findings indicating renal dysfunction and elevated serum calcium levels are noted in Table 1 which contains all pertinent laboratory data for the four cases.) Roentgen examination showed duodenal scarring and evidence of chronic rheumatoid arthritis.

A low calcium diet with non-absorbable alkalies was prescribed and in two weeks, April 5, 1950, marked improvement of the renal status and reduction in blood calcium level were observed. Subsequent examinations showed that renal function, as measured by simple clinical studies, returned to normal.

Comment. This case was discovered before the syndrome had manifested itself in its entirety. There was hypercalcemia with moderate renal damage but without phosphorus retention or alkalosis. Early in the hospital course gout and previous therapy with gold were considered as possible etiologic agents of the renal damage. The only evidence of calcinosis was the history of ureterolithiasis. The rapidity with which the kidney dysfunction may develop, as manifested by significant albuminuria, hyposthenuria and abnormal urine sediment, was demonstrated by

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the fact that only four months previously repeated examinations disclosed excellent renal function. The prompt response to removal of the offending agents was impressive.

CASE II. L. N. (N.E.C.H. No. 65-388), a fifty-two year old male, was hospitalized January 14, 1952 because of recurrent abdominal pain. Since roentgenographic demonstration of a duodenal ulcer in 1924, there had been only short, infrequent intervals during which he had been free of pain, despite daily therapy with 12 gm. of sodium bicarbonate and 1 quart of milk.

Physical examination showed hypertension (B.P. 160/100), senile emphysema and marked arcus senilis.

After one week of a strict medical regimen there was symptomatic relief and the patient was discharged with instructions for dietary and non-absorbable alkali therapy. He later revealed that he had subsisted exclusively on milk and cream for the six weeks following hospitalization and thereafter had returned to a restricted self-imposed diet and the sodium bicarbonate powders.

In August, 1952, a respiratory infection was followed by insomnia, anorexia, progressive asthenia and severe exacerbation of the abdominal pain. He had gradually increased his daily ingestion of sodium bicarbonate to approximately 100 gm. and his milk intake to 3 quarts in an attempt to alleviate the ulcer pain. In September he had noted the onset of pruritus, polydipsia, polyuria and weight loss. He was re-hospitalized October 15, 1952. Physical examination showed signs of corneal calcification (later confirmed by slit lamp examination) which led to a correct diagnosis of hypercalcemia and renal disease, previously interpreted as chronic glomerulonephritis.

Urine examination revealed 1+ albuminuria, hyposthenuria, 5 to 15 white cells per high powered field and no casts. (Evidence of azotemia, alkalosis and hypercalcemia is noted in Table I.)

A low calcium diet, non-absorbable alkalies and anticholinergic drugs were prescribed. There was rapid clinical improvement which was reflected in the laboratory studies. Because of some persistence of abdominal pain, nausea and malaise, subtotal gastrectomy was performed on November 12, 1952. After the operation he experienced no further gastrointestinal symptoms and remained asymptomatic without further therapy. His blood pressure stabilized at 120/70.

Comment. This case illustrates the typical syndrome and the marked improvement which may occur following early diagnosis and treatment. Recognition of corneal calcification led to the correct interpretation of hypercalcemia with renal dysfunction which was previously considered to be due to chronic glomerulonephritis.

CASE III. J. M. (N.E.C.H. No. 65-616), a fifty-two year old male, was admitted January 18, 1952 with a history of burning epigastric pain for more than thirty-five years. Since 1929 treatment had consisted of 2 quarts of milk and 6 to 16 gm. of sodium bicarbonate daily. In 1950 a calcified lesion of the lung, not present in 1945, was seen on the chest film. Shortly thereafter he had begun the periodic use of vitamin D for arthritis. In July, 1951, he had noted the onset of anorexia, insomnia, weakness, muscle aches, constipation and abdominal pain. These symptoms had been followed in a few weeks by pruritus and conjunctival redness.

Physical examination showed arthritis, band keratopathy and calcium deposition in the cornea and bulbar conjunctiva. The eye findings were confirmed by slit lamp examination.

Urinary abnormalities consisted of a faint trace of albumin, occasional red and white cells and calcium oxalate crystals, hyposthenuria, but no casts. Urine culture was negative. (Laboratory data showing azotemia, alkalosis and hypercalcemia are summarized in Table I.) Roentgenograms demonstrated arthritis, duodenal deformity and metastatic calcifications in the falx cerebri, lung, kidneys and soft tissues of the hands. Prior to demonstration of metastatic calcifications by x-ray and slit lamp examinations, the renal disorder was thought to be the result of chronic pyelonephritis.

The administration of a low calcium diet with non-absorbable alkalies and sodium chloride tablets resulted in definite clinical but only slight laboratory evidence of improvement in about three weeks and the patient was discharged from the hospital.

In June, 1952, there was recurrence of the epigastric pain, associated with cicatricial pyloric obstruction, necessitating rehospitalization and subtotal gastrectomy. Preoperative urine culture showed Pseudomonas aeruginosa, which remained refractory to antibacterial treatment during the next seven months.

The patient was discharged and thereafter

continued to do well for four months. However, when he was seen in December, 1952, he had lost 24 pounds of weight and showed marked lethargy, cachexia and transient episodes of psychotic behavior. He reentered the hospital on December 8, 1952.

Laboratory examinations at that time showed an increase in albuminuria, pyuria and microscopic hematuria, in addition to evidence of increasing renal failure. Therapy for uremia, chronic pyelonephritis and malnutrition was unsuccessful and he expired January 7, 1953.

Autopsy revealed chronic pyelonephritis, secondary parathyroid hyperplasia, granuloma of the lung, nephrocalcinosis and the other previously mentioned metastatic calcifications.

Comment. This case illustrates the malignant course which the syndrome may take. Evidence of metastatic calcification was present before the use of vitamin D but the latter could have further accelerated the disease process. The refractory pyelonephritis undoubtedly contributed to the renal failure.

TABLE I
BLOOD STUDIES

	Urine Max. Sp. Gr.	Urea N (mg. %)	Ca (mg. %)	P (mg. %)	Alkaline Phosphatase (B.U.)	Na (mEq./L.)	Cl (mEq./L.)	CO_2 (mEq./L.)	K (mEq./L.)	PSP 30″	PSP Tot. 2°
Case I											
Pretreatment											
3/20/50	1.010	51*	12.8	3.4	2.6	133	93	24	4.6	12	29
After withdrawal of alkali and calcium											
4/5/50	1.020	41*	10.5	3.8	...	145	103	28	4.3	....	...
2/1/53	1.025	14	10.1	4.0	1.2	138	96	31	5.1	50	100
Case II											
Pretreatment											
10/15/52	1.010	60	16.0	4.2	1.6	142	87	40	3.5	11	22
After withdrawal of alkali and calcium											
10/20/52		53	10.8	3.2	...	141	102	26	4.1	....	...
After gastrectomy											
11/10/52	1.019	23	10.2	....	...	140	100	30	4.7	18.5	41
4/17/53	1.028	29	10.0	4.2	3.0	140	100	29	5.1	32	57
Case III											
Pretreatment											
1/18/52	1.010	66	14.5	5.6	4.0	130	80	30	4.0	0	22
After withdrawal of alkali and calcium											
2/9/52	1.010	27	13.7	3.1	...	137	99	29	...	14	40
Onset of urinary infection											
6/12/52	1.007	21	13.3	5.4	1.0	137	85	39	4.2	....	13
Final admission											
12/8/52	1.010	78	9.3	10.6	...	130	102	13	4.9	0	1
1/1/53	.....	170	....	....	...	135	102	16	5.4	....	...
Case IV											
Pretreatment											
2/25/53	1.008	54	11.5	6.0	2.0	135	87	37	4.4	6	15
After withdrawal of alkali and calcium											
3/26/53	.....	68	12.8	4.4	...	134	96	29	4.5	....	...
4/30/53	1.013	59	12.5	4.0	2.0	137	94	32	4.5	10	...

* NPN.

CASE IV. S. S. (N.E.C.H. No. 71-077), a fifty year old male, was admitted on February 25, 1953, with a history of epigastric pain of twenty years' duration. This had been treated with 4 quarts of milk and 8 to 36 gm. of a

mixture of sodium bicarbonate and calcium carbonate daily for over eight years. In 1951 he had been studied in an outpatient medical clinic and was found to have a duodenal ulcer, chronic gastritis, anemia and pyuria. Seven months prior to hospitalization he had developed arthralgia and pruritus and the laboratory studies had disclosed azotemia, anemia, albuminuria, hyposthenuria and microscopic hematuria and pyuria. A diagnosis of chronic glomerulonephritis had been made and appropriate management instituted. He was admitted to the hospital in January, 1953, because of the continuation of symptoms and the observation of corneal calcification.

Physical examination revealed a poorly nourished, chronically ill patient with excoriations of the skin. Corneal calcium deposits and an ulceration of the left cornea were seen. There was tenderness in the upper abdomen and costovertebral angles. Urinalyses showed no casts. (Other laboratory data demonstrating azotemia, hypercalcemia and alkalosis are found in Table I.)

Roentgenograms showed marked deformity of the duodenal bulb and calcifications in the left subdeltoid bursa, the left renal parenchyma and in the region of the right ischial tuberosity. He was treated with a low calcium diet and nonabsorbable alkalies. Ocular pain and calcifications were treated with topical applications of a calcium chelating compound[8] with subjective and objective improvement. Attempts to lower the blood calcium by the intravenous use of these chemical agents were unsuccessful.[9]

On a constant diet containing less than 1.0 gm. of calcium per day there was no change in the high level of calcium in the serum, and the urinary calcium excretion varied between 90 and 377 mg. per day. Despite the absence of elevation of the serum level of alkaline phosphatase and bony changes by x-ray, it was believed that parathyroid exploration was indicated. This was done April 24, 1953. All four parathyroids were examined. The glands were not grossly enlarged and microscopic study revealed a few tiny foci of epithelial overgrowth suggesting a degree of overactivity.

At the time of discharge to the outpatient department (April 30, 1953) he was entirely free of abdominal pain but there was no significant improvement in renal function.

Comment. This case demonstrates some of the difficulties that may be encountered in the differential diagnosis of both the renal dysfunction and the hypercalcemia. It also suggests the inefficiency of some of the newer therapeutic compounds in lowering blood calcium in the presence of advanced renal dysfunction.

OBSERVATIONS

The clinical findings in all four cases had striking similarities. All were white males with a history of peptic ulcer for over twenty years, treated with 1 to 4 quarts of milk and large amounts of absorbable alkalies. After at least eight years of intensive therapy symptoms secondary to hypercalcemia and renal dysfunction appeared: muscular weakness, lassitude, anorexia, nausea, vomiting, weight loss, constipation, polydipsia, polyuria and pruritus.

Physical examination revealed malnutrition, pallor, and in one case moderate hypertension, which returned to normal during hospitalization.

The most reliable physical sign of this disorder is ocular calcification, present in three cases and consisting of keratopathy and calcium deposits in the conjunctiva. The former may be mistaken for arcus senilis. On closer inspection, however, individual minute corneal calcifications can be distinguished forming a circle broader and more centrally located than that characteristic of arcus senilis. The nasal and temporal areas of the circle show the greatest concentration of calcium. Although these eye signs may be found in other causes of hypercalcemia,[10] the history of excessive calcium ingestion should aid in differentiation.

Laboratory examinations of the blood disclosed azotemia, normochromic and normocytic anemia, hypercalcemia, normal or elevated phosphorus, normal alkaline phosphatase and potassium with low chloride levels. The total bicarbonate content of the blood was above normal in three of the four cases. The carbon dioxide tension of the plasma was elevated to 60 mm. Hg in Case IV but data were not available in the other cases. Abnormal renal function was manifested by a low fixed specific gravity, albuminuria, granular casts, occasional red and white blood cells, nitrogen retention and a markedly decreased excretion of phenolsulphonephthalein dye.

The differential diagnosis has been reviewed in previous papers[5,6] and includes: primary hyperparathyroidism, acute osteoporosis, hypervitaminosis D, sarcoidosis, multiple myeloma, renal rickets and generalized carcinomatosis

with metastatic bone involvement. Thorough study disclosed no evidence that these conditions were present in the cases here reported. It is important that the kidney disorder be differentiated from chronic glomerulonephritis and other causes of irreversible uremia.

The development of this entity appears to depend upon either hypercalcemia or alkalosis or both. Renal damage may occur in association with hypercalcemia and increased urinary calcium excretion from a variety of causes.[11a] Increased calcium ingestion in normal adult subjects can cause hypercalcuria.[11b,12] The long period of excessive calcium intake suggests that hypercalcuria develops early in the course of this syndrome, and may have initiated tubular calcification with subsequent renal impairment. On the other hand, in chronic renal disease the ability to excrete a calcium "load" is decreased,[13] and it is probable that the hypocalcuria observed in this disorder[5] is a late finding resulting from renal damage. An analogous reduction in urinary excretion of calcium has been reported in hyperparathyroidism after the development of renal impairment.[14] The secondary parathyroid hyperplasia seen in Cases III and IV probably intensified the hypercalcemia and metastatic calcification and accelerated the renal failure.

Alkalosis is not a necessary prerequisite for nephrocalcinosis[15] nor probably for the development of this syndrome as shown by Case I. However, if alkalosis is present it may contribute to renal dysfunction.[1–4,16,17] Burnett et al.[18] by detailed studies have shown that such renal derangement may persist for long periods. Once established, the alkalosis may become prolonged, perhaps in part due to potassium depletion,[19] and also through elevation of the partial pressure of carbon dioxide.[20] The latter apparently increases the renal reabsorption of bicarbonate and thus sustains the elevated serum bicarbonate level. Normal serum potassium values in these and other reported cases give no indication of total body potassium depletion, which is known to occur in certain cases of alkalosis.[19,21–23] If such depletion occurs, it may be a significant cause of reversible renal damage.[24]

Recovery depends on the extent of renal impairment. This probably is initially reversible as shown by Cases I and II, who became entirely asymptomatic and showed return to practically normal renal function. (Table I.) The need for early diagnosis is stressed by Cases III and IV whose renal damage was not reversible, and this resulted in uremic acidosis and death in Case III and a poor prognosis in Case IV.

Treatment of this disorder should be aimed at correcting existing abnormalities. Absorbable alkalies should be discontinued and a low calcium diet instituted in addition to the indicated medical or surgical management of the peptic ulcer. Disappearance of the alkalosis may occur if the alkali "load" is reduced but this may require the use of acidifying salts or potassium.[25] Correctible urinary tract disorders, especially infection and obstruction, should be looked for and treated. The ocular lesions may improve with local application of calcium-binding agents as did those in Case IV. These agents give promise for systemic therapy but no definite conclusions about their efficacy seem warranted as yet.

Attention should be focused on the prevention of this disorder. This can be achieved by the proper management of peptic ulcer which precludes the prolonged use of absorbable alkalies and excessive calcium.

SUMMARY

Four cases of chronic renal failure following prolonged treatment of peptic ulcer with milk and absorbable alkalies are described. The finding of ocular calcification led to the immediate clinical differentiation of this entity from other forms of kidney disease in three cases.

In two cases renal function returned virtually to normal after withdrawal of the offending agents.

The importance of suspecting remediable kidney failure in patients with chronic peptic ulcer is stressed. Recent concepts of pathogenesis and treatment are discussed.

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Small Intestinal Function in Patients with an Ileostomy*

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THE relatively inaccessible position of the small intestine in the normal human subject has limited observations on the factors concerned in its functioning. Roentgen studies using opaque meals are concerned entirely with motor activities and depend for their interpretation largely on the subjective impressions of the investigator. Intubation studies from above have the disadvantage of subjecting the patient to an uncomfortable procedure, the emotional implications of which on subsequent observations are difficult to evaluate.

Since the days of Beaumont, studies on subjects with fistulous openings into various parts of the gastrointestinal tract have yielded much valuable information. The work of Wolf and Wolff[1] on a man with a gastric opening and the observations of Grace, Wolf and Wolff[2] on colonic fistulas have contributed greatly to our understanding of certain factors concerned in the normal and abnormal physiology of these organs. It is the purpose of this paper to present certain observations on the small intestine of patients with an ileostomy in whom the fistulous opening permitted direct visualization of the ileal mucosa and allowed retrograde intubation of the ileum thus making possible balloon-kymograph studies with the least possible discomfort to the subject. By these technics observations on the following conditions were made: (1) a comparison of recorded wave patterns with ileal propulsive activity; (2) the effects of emotional stress; (3) changes in ileal blood flow as reflected in mucosal color; (4) mucosal fragility; (5) the effects of eating and (6) the influence of drugs.

METHODS AND MATERIAL

All subjects reported to the laboratory after a fast of at least six hours and without medication for twelve hours. They were placed in a comfortable supine position in bed and care was taken to assure that they remained awake during the procedure. The ileum was intubated in a retrograde fashion through the ileostomy with a tube containing a condom rubber balloon (approximately 3 inches long) and stiffened with a wire spring. The tube was introduced for a distance of 8 to 12 inches. It was connected to a water manometer provided with a float so that kymographic tracings of motility could be recorded from the balloon. The latter was inflated with air to a pressure of approximately 4 or 5 cm. water. The tube-balloon arrangement did not interfere with propulsion in the ileum, since liquid fecal contents and gas were discharged intermittently during the observation period.

Mucosal color change was evaluated by comparison with a Talquist hemoglobin scale under constant artificial illumination. Richards et al.[3] have shown that gastrointestinal mucosal color reflects degree of blood flow as determined by the thermal gradientometer technic, and measurement of mucosal color change has been utilized previously in the study of gastric and colonic fistulas to assay circulatory changes.[1,2]

Mucosal fragility was quantitated by application to the ileal bud of a soft rubber tube containing a small opening on which constant suction equivalent to 200 cm. water was exerted by means of a pump. Readings were taken at thirty-second intervals and the "end point" was the production of a round reddened area resembling a submucosal hemorrhage as described by Grace et al.[2]

Three or more studies were carried out on each of five subjects. (Table I.)

RESULTS

Correlation of Recorded Wave Pattern with Ileal Propulsive Activity. Twenty-six kymographic tracings were made of ileal motility in the five

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subjects. An attempt was made to correlate the recorded wave pattern (interpreted according to the classifications of Templeton and Lawson[4] and of Adler et al.[5]) with the ileal propulsive activity, as demonstrated by the expulsion of feces or flatus from the ileostomy. In no instance did the records show typical type II waves. The small frequent type I waves were found never to be associated with active propulsion, although occasionally a small slow seepage occurred when only this type of activity was being recorded. It is possible that this may have been the result of peristaltic activity higher up in the intestine proximal to the balloon. Whenever there was a forceful expulsion of feces or flatus, it was associated with waves of the type III variety. This type of activity, however, was frequently seen unassociated with ileal expulsion. Ileal expulsion in a typical case is shown in Figure 3.

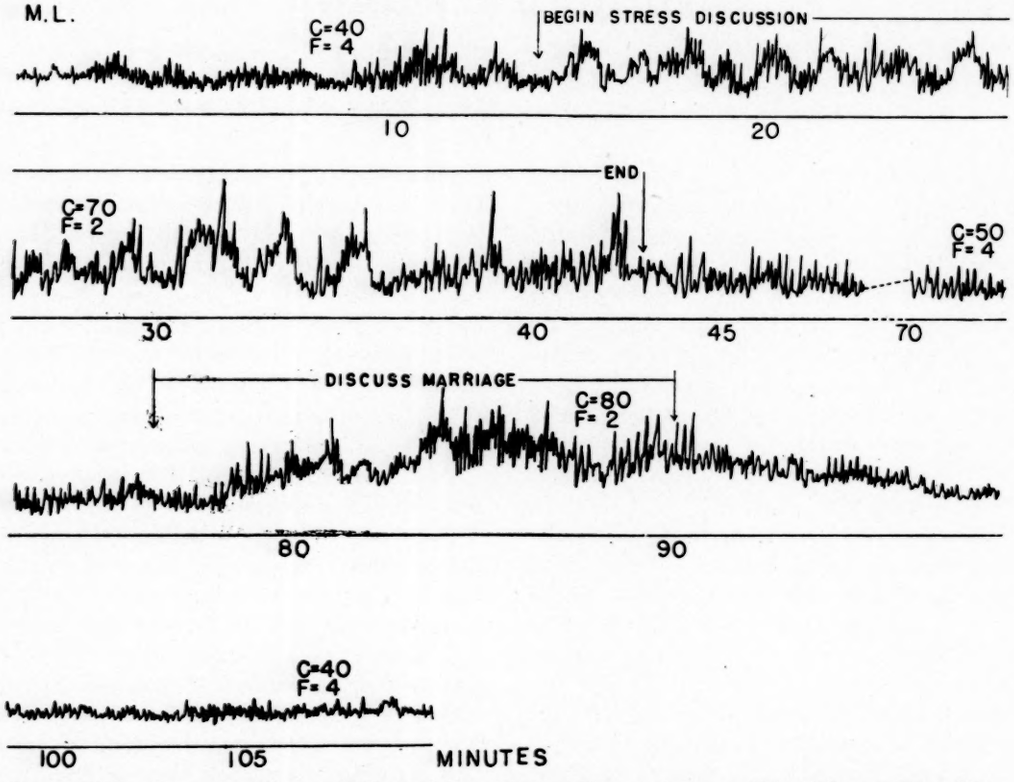

FIG. 1. Effect of emotionally stressful interview on ileal motility and mucosal blood flow and fragility. C, mucosal color compared to Talquist scale; F, minutes required to produce mucosal lesion by suction.

TABLE I
DESCRIPTION OF SUBJECTS

Name	Age and Sex	Indication for Ileostomy	Duration of Ileostomy (yr.)
M. L.	19, M	Ulcerative colitis	⅔
S. L.	31, F	Ulcerative colitis	11
W. B.	20, M	Ulcerative colitis	1½
R. S.	30, F	Ulcerative colitis	1½
S. Z.	26, F	Polyposis coli	4

Effect of Emotional Stress. On questioning, each of the subjects admitted that his ileostomy "ran more freely" during periods of emotional conflict, and that abdominal cramps and "gas pains" seemed more common in such circumstances. An attempt was made to document these observations in four of the patients (M. L., S. L., W. B. and S. Z.) by observing the changes in ileal function during an emotionally stressful interview. A typical result is demonstrated in Figure 1. The patient (M. L.) was a conscientious dependent Italian boy whose bloody diarrhea had begun within twenty-four hours after an auto accident. The episode was of tremendous import to him because he had been riding against the advice and without the knowledge of his rigidly disciplinarian parents.

A progressively downhill course during the next two years necessitated iléostomy to which he adjusted poorly. He became depressed, felt that "life was over" for him and expressed suicidal tendencies. Emotionally labile, he relived vividly during this period. Again ileal motility was increased with evidence of heightened tonus but with no expulsive activity. A sympathetic discussion of his problems and changing the conversation to a neutral topic again produced a

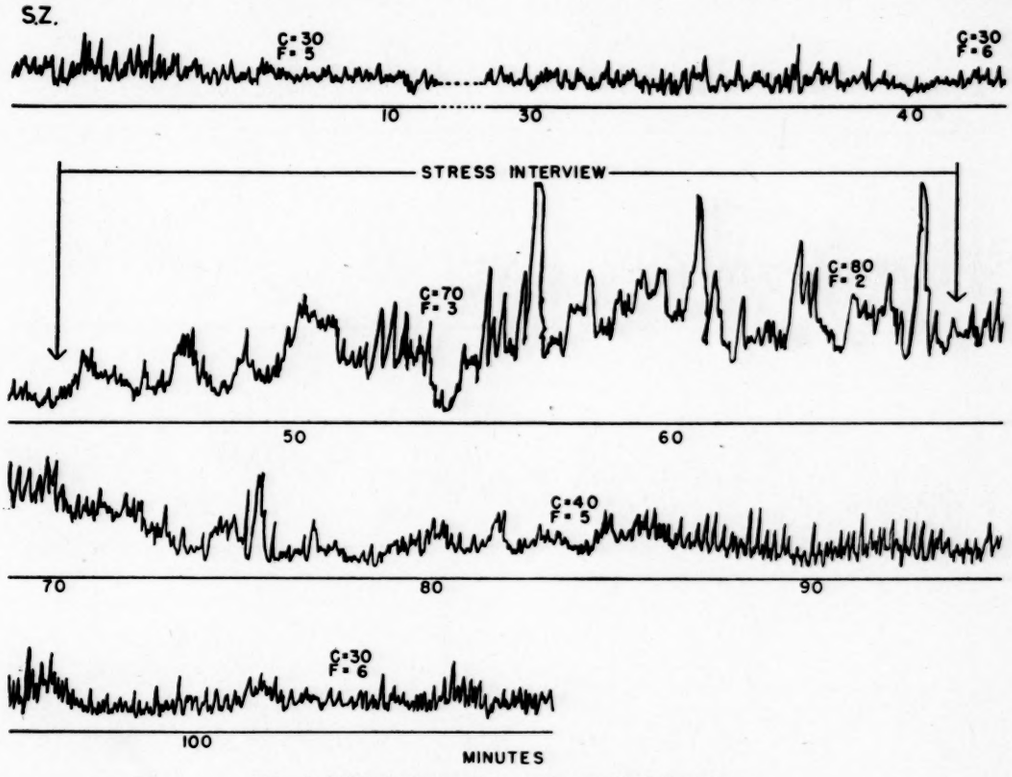

FIG. 2. Effect of stress interview on ileal function.

in his expressions and actions the conflicts which troubled him.

During the test a neutral conversation of fifteen minutes was replaced by a discussion of his accident. He became uneasy and afraid and said "I was scared to death and terrified of what my parents would say when they found out." He seemed resentful of his parental domination. During this period ileal activity increased and several spurts of fecal contents were noted. Changes in mucosal color and fragility will be commented on later. The subject of conversation was now changed to a neutral one—automobiles, a hobby of his. Motility decreased as he became more relaxed and at ease and ileal discharge ceased. Later the subject of his adjustment to ileostomy was introduced. He became depressed and seemed on the verge of tears. "Now I'll never be able to amount to much," and "who would ever want to marry a crippled man with a smelly bag" were typical comments quieting effect. At the end of the experiment he volunteered the information "my stomach always feels worse when I think about those things."

Another example is shown in Figure 2 recorded from a patient whose ileostomy was performed because of multiple polyposis of the colon. A sensitive, "nervous" woman, she was resentful of the fact that failure to marry (which she attributed largely to her ileostomy) required her to assume the responsibility for making her own livelihood by secretarial work. Introduction into the conversation of these emotionally charged topics, in an unsympathetic fashion, produced overt resentment, flushing of the face and a marked increase in ileal motility and propulsive activity.

Similar results were obtained in the other two patients studied. In all, evident emotional disturbance was accompanied by ileal hypermotility, often by expulsion of flatus or liquid

feces, and by changes in mucosal color and fragility to be described later. Indeed, the "control" motility pattern recorded in different experiments seemed to vary with the mood in which the subject reported to the laboratory.

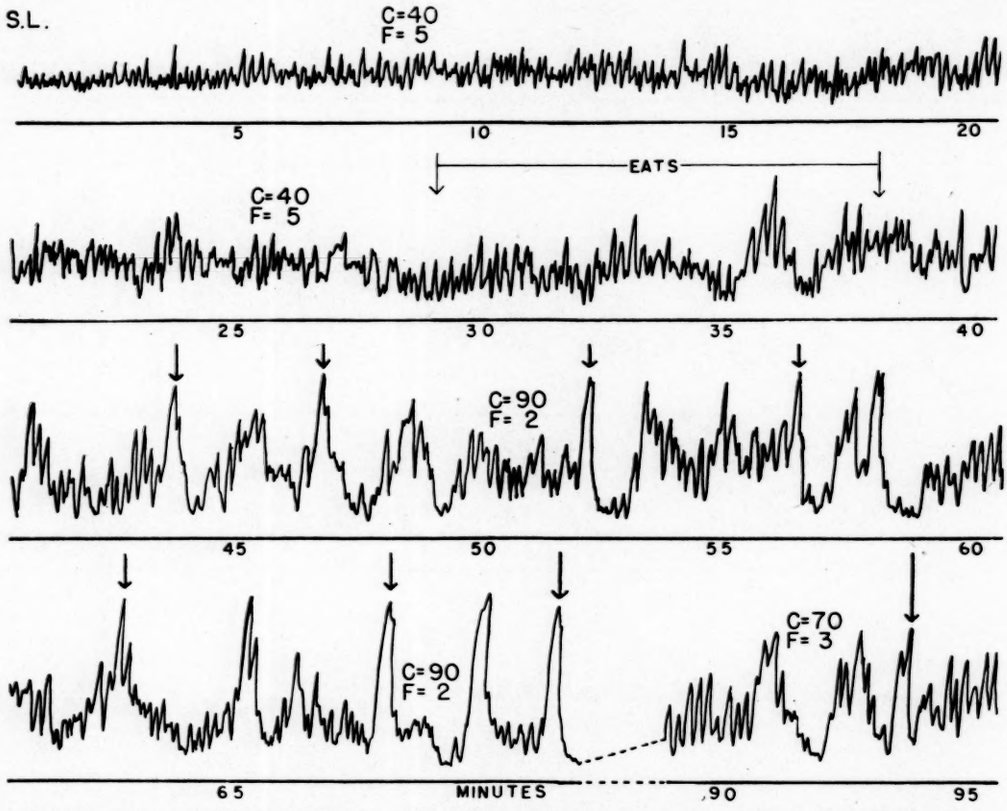

FIG. 3. Response of ileum to the ingestion of food. Arrows represent expulsion from ileostomy.

When at ease and cheerful it was predominantly the small type I variety; but when the patient seemed tense or anxious concerning the experimental procedure, it was apt to demonstrate more frequent type III waves and expulsive action.

Changes in Ileal Blood Flow as Reflected in Mucosal Color Change. The resting mucosal color usually varied from 30 to 60 on the Talquist scale and ranged from a moderate pink to a brilliant red. Under conditions of hypermotility, whether induced by emotional stimuli or eating, the color of the ileostomy bud deepened, often to a deep cardinal red, representing a reading of 70 to 90 on the scale. These changes are illustrated in Figures 1, 2 and 3. Reduction in hyperactivity to control levels was accompanied by a concomitant reduction in depth of mucosal color. In those instances in which a control period was followed by the administration of an antispasmodic drug, reducing ileal activity, the mucosal color change was minimal, although in the direction of a reduction in color when it occurred. As in the case of motility, the basal mucosal color was apt to be increased when the subject reported to the laboratory in circumstances indicating emotional upset.

In two subjects introduction of a "baby" proctoscope into the ileum through the ileostomy revealed that the more proximal portions of the mucosa participated in the color changes observed externally, so that color of the mucosa of the bud is considered an accurate reflection of blood flow through the distal ileum, at least.

Mucosal Fragility. Application through a rubber tube of a negative pressure of 200 mm. H_2O to the ileal mucosa of the subject in the control state resulted in the production of lesions resembling submucosal petechiae or actual submucosal hemorrhage in from three to six minutes. When the ileum was made hyperactive, whether by emotional stress or eating, a similar lesion could be produced in an appreciably shorter period of time, generally one to two minutes. Typical results are shown in Figures 1,

2 and 3. In no case was increased fragility observed unaccompanied by both hypermotility and hyperemia. In those cases in which anticholinergic drugs were employed to depress ileal activity, no real change in mucosal fragility was observed. (Fig. 4.)

ingestion had begun. In one subject the food was presented and preparation made for eating. Ileal hyperactivity occurred and lasted for ten minutes before actual ingestion was permitted. It then persisted without augmentation following ingestion of the meal. This occurred when the

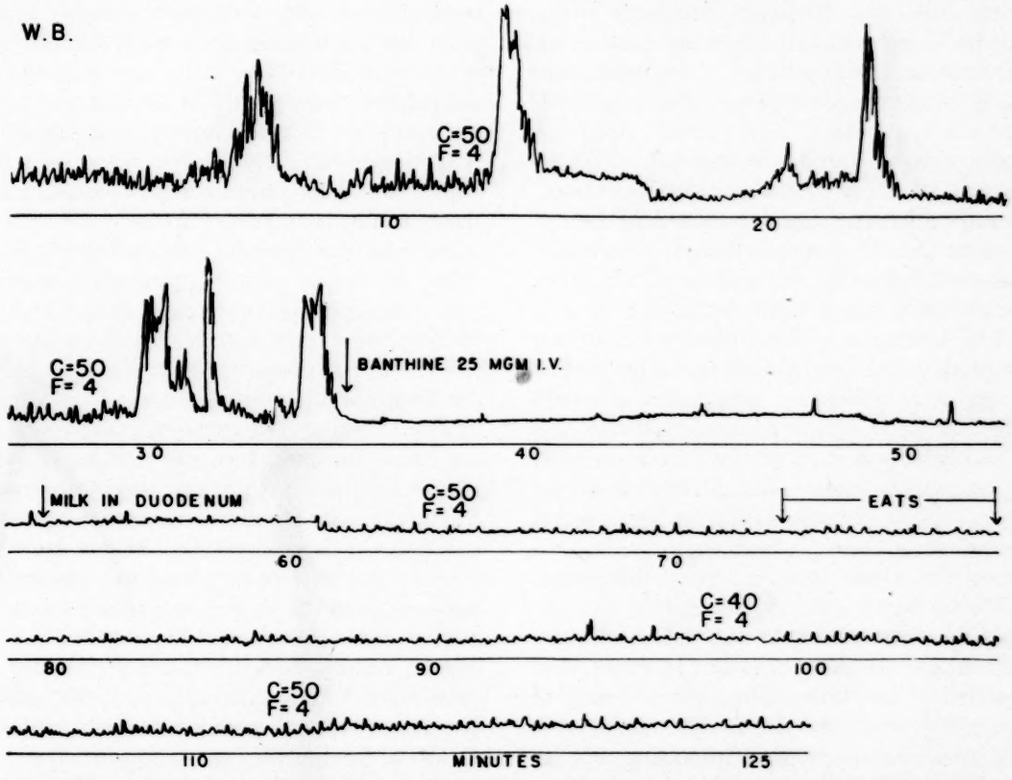

FIG. 4. Block of the "gastroileal reflex" by intravenously administered banthine. Note also that there is no response to the introduction of milk into the duodenum. No change occurs in mucosal blood flow or fragility.

Effect of Eating. Each of the subjects stated that ingestion of food was almost always followed by some increase in expulsive action from the ileostomy. To test this experimentally, seven observations were made in the five patients. After a control period during which the usual observations on motility, mucosal color and fragility were made, a sandwich and 240 ml. of milk at room temperature were ingested. In each case a marked hyperfunction of the ileum occurred with increased segmental activity and expulsion of liquid feces and gas, hyperemia and some increase in fragility of the ileostomy bud. A typical example is illustrated in Figure 3.

In all cases these changes occurred during or immediately following the meal and in several they began during the preparation for eating when the food was in sight but before actual subject was quite hungry and anticipated with relish the particular sandwich offered him.

In order to determine whether similar small bowel hyperactivity could be obtained in normal subjects following eating, two additional patients were intubated through the mouth with a Miller-Abbott tube. In one the balloon was in the jejunum, in the other in the lower ileum. In both increased segmental motility was recorded from the bowel in response to ingestion of a test meal. In these subjects as well as in those with ileostomies the heightened degree of intestinal activity persisted for at least sixty minutes following the meal at which time the observations were terminated.

Influence of Drugs. The effect of orally and intravenously administered atropine and banthine® on ileal hyperfunction in response to

eating was studied in four patients, in three of whom comparative studies with the two orally administered drugs were made. Atropine sulfate was given orally in a dosage of 1 to 1.2 mg. and banthine in a dose of 100 mg. In each case marked xerostomia was produced. In no instance, however, was the ileal response to eating completely blocked, although with both drugs considerable reduction in activity occurred, with decrease in ileal discharge. The increase in hyperemia and fragility was only partially blocked.

Atropine sulfate (0.6 mg.) was given to two patients and banthine (25 mg.) to one patient, intravenously. Marked xerostomia and tachycardia occurred in each instance. Intestinal motility was markedly decreased in all three cases but without significant reduction in mucosal color or fragility. The response to eating was completely blocked in each instance. In the patient given banthine an attempt was made to determine if the suppression of function following eating was due to gastric retention with slower passage of orally ingested food into the duodenum. Eight ounces of milk were injected into the intestine through a duodenal tube. No stimulation of ileal activity was produced. (Fig. 4.)

In only one instance (patient S. L.) was the effect of drugs on the response to emotional stress studied. This patient was given 1 mg. of atropine orally with the usual side effects. No suppression of hyperactivity (including hyperemia and hyperfragility) was produced when she was subjected to an emotionally charged interview.

COMMENTS

The utilization of patients with ileostomies for observations on small intestinal function provides, in the human subject, a direct method of approach otherwise difficult to attain, and permits comparison with similar studies previously reported on gastric and colonic fistulas.[1,2] Reservations in applying the results of such studies to the whole of the small bowel or to the nonfistulous intestine must be kept in mind. However, the agreement between much of the data so obtained and the results of studies employing other technics in intact individuals tend to validate the physiologic significance of such observations.

A unique opportunity is afforded to correlate kymographic wave pattern with propulsive activity as directly observed. Apparently type I waves are not associated with active propulsive activity in the segment, although peristalsis in more proximal portions of the bowel may lead to slow discharge from the ileum during the recording of this type of wave alone. Type III waves, however, appear to be potentially propulsive, although their effectiveness in this regard apparently depends on the availability of material delivered to the active segment by the propulsive movements of proximal portions of the intestine. These observations are in accord with those of Ingelfinger and Abbott[6] and Chapman and Palazzo[7] who have correlated wave pattern with barium propulsion on fluoroscopy of the intact small intestine, and with those of Posey and Bargen[8] who studied the problem in patients with ileal and colonic fistulas. The inability to demonstrate type II waves in recordings from the ileum corroborates the findings of Code et al.[9]

The relation between emotions and gastrointestinal function has received much attention of late. Objective studies to elucidate these interrelations in the small bowel, however, have been sparse. As early as 1904 Macewen[10] studied several patients with fistulous openings into various portions of the intestinal tract. He reported that "in a case where the anterior wall of the cecum had been removed (by an explosion) the ileocecal valve and the appendicular orifice being exposed, after recovery from the shock several observations were made. It was seen that his will power had no effect upon the control of the ileocecal valve, but one day when he was much disturbed by the reception of 'bad news' which could not be kept from him, and after which he said he had indigestion or was 'bilious,' the secretion in the cecum was at first very watery and then the surface became drier than at any previous time and apparently the contents of the small intestine were more quickly evacuated and overflowing, gave rise to smarting and irritation on the sides of the wound." This same stimulating effect of emotional tension on small bowel activity has been observed by Weeks[11] who studied the exposed ileum of a wounded Arab. "Much excitement on the ward" occasioned by the admission of a number of unruly wounded men produced "much small bowel activity (as active as it had ever been observed)."

Emery[12] has presented some clinical observations on a patient with an ileostomy showing

that hypermotility of the ileum is associated with certain symptoms suggesting the "irritable colon" syndrome. Golden[13] has reported that an angered rat, subjected to x-ray examination, has shown narrowing and segmentation of the barium-filled small bowel. He also cites the case of a woman who "became emotionally upset and began to weep during the course of a small intestine study: the small intestine, which up to that time gave the usual continuous even calibered barium shadow, then showed definite segmentation." In certain cases of diarrhea Golden reports a purely functional disturbance consisting of rapid transit time through the small bowel (especially the jejunum and ileum), narrowing of the lumen, and the presence of numerous spastic contractions.[14]

Martin[15] has observed areas of spasm in the ileum with proximal "ileostasis" in certain individuals exhibiting anxiety tension states and reports disappearance of this phenomenon following adequate psychotherapy. Ingelfinger and Abbott[6] have noted the recording of large contraction waves from the small bowel of patients intubated with a Miller-Abbott tube in whom nausea and emotional distress attended the intubation procedure. Recently Roth et al.[16] have reported increased jejunal motility and tonus in a number of patients studied with a Miller-Abbott tube when subjected to stressful interviews. They have commented on the difficulty of assessing emotional states in patients subjected to the discomfort of oral intubation.

The present experiments confirm by direct observation the stimulatory effect of emotional stress on ileal function. Not only is motor activity increased under such circumstances but hyperemia and increased mucosal fragility are produced as well. The possible relationship of the turgid, more friable mucosa associated with tension states to the actual organic damage seen in regional enteritis remains a fascinating but as yet unsolved question. There can be no doubt, however, as to the role of emotional factors in the etiology of at least some of the functional disturbances of the ileum and probably of the remainder of the small bowel as well. While the data reported here were obtained chiefly from subjects with ulcerative colitis, similar findings in the girl with polyposis coli indicate that the responses observed are not limited to the colitis patient.

Previous direct studies on fistulous human subjects[1,2] have demonstrated that in both the stomach and colon emotional experiences of anger, resentment and hostility are characterized by hyperfunction whereas the reverse feeling states of sadness and dejection are attended by hypofunction of these organs. In our patients emotional stress of either type was associated with hyperfunction of the ileum. Perhaps the experiments have not been of sufficient extent, or perhaps we have been unable to assess clearly enough the subtle shades of emotional feeling overtly manifested by our subjects, but hyperfunction of the ileum has been the response of all to the production of emotional tension of any type. Roth et al.[16] have similarly been unable to correlate the pattern of small intestine motility with any specific emotion in their patients.

The stimulating effect of food ingestion on bowel motility is well known. Macewen[10] was among the first directly to observe this phenomenon in the colon and ileum of the human subject; and Weeks[11] reported that, in his Arab patient, the ingestion of food caused "moderate small bowel activity" as observed at twenty, thirty, forty-five and sixty minutes after a meal. In observations on dogs Henricksen and Ivy[17] noted increased ileal activity after eating, with rapid passage of material into the colon "almost but not completely emptying the small intestine within 15 minutes after the animal had started to eat."

There is some dispute as to whether, in the dog, these reflexes can be stimulated only by the actual ingestion of food or whether the sight and smell of food can initiate them psychically.[17–20] The observations made in this study indicate that hyperfunction of the ileum is a regular occurrence in man in response to the ingestion of food and demonstrate that, at times, and in at least some individuals it can be initiated through psychic stimulation alone. As in the case of emotional stimulation, hypermotility in response to eating is accompanied by increased mucosal blood flow and fragility.

It is interesting to speculate on the utility of this response in the animal economy. Certainly it serves to clear the small bowel for food incoming from the stomach and to empty the non-absorbed residue into the colon. In addition, there is evidence both from indirect and direct methods of study[21,22] suggesting that segmental hyperactivity of the small bowel in the human is associated with an increase in the absorption rate. Thus ingestion of food might well prepare the intestine by stimulating activity

designed to provide optimal conditions for food absorption and its passage along the gut.

The depressant action of atropine[23–25] and of banthine[26,27] on small intestinal motility has been amply demonstrated. Our results confirm these studies but demonstrate the decided difficulty in blocking the effects of excitatory stimuli, such as eating, even with large oral dosages of these drugs. Oral administration of clinically used doses of these medications may therefore be expected to relieve but not to abolish completely the bothersome ileal hyperactivity which stimuli such as eating evoke in these patients.

The demonstration of complete blockade of the eating response by a large intravenous dose of atropine or banthine has theoretic interest concerning the mechanism of the response. Atropine is said to produce its inhibitory effect on smooth muscle either by preventing attachment of acetylcholine to the effector cell or by preventing its reponse to acetylcholine attachment.[28] Banthine apparently affects the end organ in the same manner.[29,30] Because there is no interference with the local or intracellular release of acetylcholine, parasympathetic stimulation continues to excite the intestine after atropinization.[28,31] Thus the complete block of ileal hyperactivity in response to eating by the intravenous doses of anticholinergic drugs used may well indicate that the mechanism of the "gastro-ileal reflex" resides in other than extrinsic reflex parasympathetic stimulation of the bowel. This possibility seems in agreement with the evidence that in animals the intestinal hyperactivity induced by feeding is not abolished by vagotomy but that any interruption of the continuity of the bowel (as in a Thiry-Vella loop) abolishes the augmentory effect of feeding even though extrinsic nerves to the loop remain intact.[32,33] Perhaps the effector nerves in the "reflex" reside in the intrinsic bowel plexuses or perhaps Youmans[33] is correct when he states that the "gastro-ileal reflex" is "probably simply the propagation of peristaltic waves from the stomach along the entire length of the small bowel." If the latter hypothesis applies, the effect of atropine must reside in abolition of gastric motor stimulation following eating and the "psychic" invocation of the reflex could obtain through enhancement of stomach contractions. Both of these phenomena have been shown to occur by Wolf and Wolff.[1]

In the one case studied atropine failed completely to affect the stimulatory response to emotional stress. The ineffectiveness of certain anticholinergic drugs to block the hyperactivity of the stomach and colon produced by stressful life experiences has been documented[34,35] previously and has been interpreted by Kern et al.[35] as supporting the hypothesis that excessive motor activity of "functional" gastrointestinal disorders is probably dependent upon stimulation by extrinsic nerves. This phenomenon may help to explain the unsatisfactory clinical results obtained in the treatment of such intestinal conditions with anticholinergic drugs.

SUMMARY AND CONCLUSIONS

1. Observations are reported on the small bowel function of five patients with ileostomies studied by direct visualization and retrograde intubation.

2. Emotional stress produced ileal hypermotility, hyperemia and mucosal hyperfragility, demonstrating the participation of the small bowel in the response to stressful life situations previously documented for the stomach and colon.

3. Eating, or in some cases the anticipation of food, likewise resulted in ileal hyperfunction.

4. The effect of anticholinergic drugs in modifying these responses is described.

5. The implications of these results as to the mechanisms involved and their clinical and physiologic significance are discussed.

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Review

Embolic Mycotic Aneurysms, A Complication of Bacterial Endocarditis*

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ALTHOUGH mycotic aneurysms are commonly listed as complications of bacterial endocarditis, only occasional case reports or limited reviews have appeared in the English literature since the extensive study by Stengel and Wolferth in 1923. When it became apparent that this was the last complete review, a tabulation and analysis of the cases reported since 1923 was undertaken.

Although mycotic aneurysms may result from bacterial invasion of the vessel wall from without or from within, our interest lay in mycotic (bacterial) aneurysms of embolic origin complicating bacterial endocarditis. We have therefore excluded all cases involving the proximal arch of the aorta because it has been impossible to decide from the data presented whether these were due to direct extension from a diseased valve or were embolic in origin. We have made no attempt to review the discussions of the histopathology of mycotic aneurysms, limiting ourselves primarily to the clinical aspects and their complications.

The following reports of two proven cases and one probable case of mycotic aneurysm from our own recent experience will serve to illustrate the clinical picture.

CASE HISTORIES

CASE 1. *First admission:* G. M. H. D34094 (July 12 to September 18, 1950). A twenty-eight year old colored male laborer was admitted with a twenty-four-hour history of headache, non-productive cough, profuse sweating, sudden hoarseness and weakness in the left leg.

On physical examination his blood pressure was 108/50 bilaterally, pulse 110, respiration 20, temperature 101°F. He appeared acutely ill and was sweating profusely. There were no petechiae; his fundi were normal. Oral hygiene was poor and there was moderate pharyngitis. No meningeal signs were present. Dullness and rales were noted at the right base posteriorly. The cardiac apex was just inside the anterior axillary line in the fifth intercostal space. The first mitral sound was snapping and there was a grade 3 harsh systolic murmur in the second right intercostal space, radiating into the vessels of the neck. The second aortic sound was not heard, and along the left sternal border there was a grade 2 high pitched blowing diastolic murmur. Neurologic examination revealed left facial weakness, hoarseness, dysarthria, left-sided weakness with jerky incoordinated movements. The deep tendon reflexes were hypoactive in the left upper extremity and hyperactive in the involved lower extremity.

His mother reported that two months earlier his knees had been swollen and painful for five days. He had improved without therapy but periodically complained of numbness in the extremities. There was no known history of heart disease, venereal disease, recent dental work or respiratory tract infection.

Initial laboratory studies revealed hemoglobin 13 gm., hematocrit 39, sedimentation rate 55 mm./hr., white blood cells 8,750, polymorphonuclears 88, lymphocytes 12; venous pressure measurements and circulation times were normal. Urine: specific gravity 1.022; microscopic: occasional hyaline cast, 8 to 10 red blood cells. Sputum culture: 4 plus alpha hemolytic streptococcus, occasional colony of beta hemolytic streptococcus. Blood cultures were negative. Total protein 5.9 gm., albumin 3.0, globulin 2.9. The Kahn test was negative. Spinal tap: 100 white cells/mm.^{3}, sugar 50 mg. per cent, protein 88 mg. per cent, chlorides 723 mg. per cent, colloidal gold 5543210000; Kahn test and culture were negative. X-ray of chest revealed slight mottling at the right base. The lung fields were otherwise clear and the

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diaphragms normally outlined. The heart was enlarged in its transverse and long diameters. The aorta was within normal limits. An electrocardiogram was compatible with left ventricular hypertrophy.

Multiple blood cultures were drawn and he was treated symptomatically. He continued febrile, ranging between 101° and 104°F. Leukocyte counts ranged between 7,000 and 14,000. Several urine specimens showed clumps of white cells and occasionally 10 to 15 red blood cells per high power field. A systolic thrill became palpable in the aortic region and some observers thought they could hear a rumbling apical diastolic murmur. Because of increasing fever and toxicity, and in spite of thirteen negative blood cultures by the end of the second day, one million units of crystalline penicillin was begun intramuscularly every two hours. The presumptive diagnosis was cerebral embolism complicating bacterial endocarditis.

The first of many petechial hemorrhages was noted in the right conjunctival sac on the fourth hospital day. The aortic diastolic murmur developed a slightly musical quality. His temperature dropped abruptly below 101°F. and during the next week slowly came down under 100°F. where it remained. On the fifth hospital day it was noted that there was tenderness in the right calf and pulsation of the right dorsalis pedis artery was greatly diminished.

With the passage of time, the aortic diastolic murmur increased in intensity, the diastolic pressure fell slightly and a moderate anemia developed.

Twenty-one blood cultures and one bone marrow culture—grown both aerobically and anerobically—were sterile. At the end of the first week penicillin was reduced to 1 million units every three hours and continued for seven weeks.

He required narcotics for relief of pain in the right calf. The popliteal pulse was strong but pulses below this point were obviously diminished. The right leg measured 1 to 2 cm. greater than the left. Following paravertebral block he had relief of his pain and a slight increase in the pulses in the right leg. The edema increased and the superficial veins became visible. Although he obtained some relief of pain with TEA® given intravenously, intramuscular hexamethonium® proved to be more effective. It was believed he had suffered another embolic episode and had developed an associated thrombophlebitis.

With physiotherapy, function on the hemiparetic side improved and edema of the leg subsided. He remained afebrile, urines cleared and leukocytosis resolved.

Seven weeks after admission a pulsating mass was noted in the posterior right calf, just below the popiteal space. It was difficult to outline but the pulsations were forceful and a thrill was palpable. This mass was thought to be a ruptured aneurysm with a false sac. Arteriography was unsuccessful and the patient refused a repeat study. Surgery was advised but declined and he was discharged nine weeks after admission to the Cardiac Clinic.

Second admission: D39363 (September 28, 1950). The evening of admission he suddenly developed pain and a feeling of numbness in the right leg and was admitted at 2:00 A.M. He had improved to a point where he was able to walk without crutches.

On examination temperature was 101°F., blood pressure 112/60, pulse 110. Examination of the heart revealed no change. The liver was palpable four fingerbreadths below the right costal margin. Both feet were cool and there was anesthesia of the sole of the right foot. He was treated symptomatically and his presenting complaints disappeared.

At 10:00 A.M. he was noted to be cold, tachypneic, pale and extremely anxious. His neck veins were distended and there were a few rhonchi and rales at the right base. Heart sounds were not diminished. The right leg was a dusky color, cool, swollen and tense, with no pulsations of the arteries including loss of the abnormal pulsation previously described. White blood count was 17,000, polymorphonuclears 79, lymphocytes, 18, monocytes 3, hemoglobin 9.5 gm., hematocrit 24, icterus index 15. An electrocardiogram showed no significant changes. A few seconds after administration of morphine sulfate he vomited coffee-ground material and died.

At postmortem examination the heart weighed 550 gm. and showed left ventricular hypertrophy. The mitral valve was normal except for two or three thickened nodules along the free margins of the valves. The aortic valvular structures were almost completely destroyed by ulcerogranular vegetations.

On cut section the pulmonary parenchma was a light pink in color and there was no evidence of bronchopneumonia or pulmonary edema. Sections of the pulmonary artery revealed no

thrombi or emboli in the pulmonary artery or arterioles. Sectioning of the bronchi revealed a small amount of a red-tinged fluid.

The right lower extremity was dissected and in the region of the popliteal space a soft, fluctuant mass was seen underlying the gastrocnemius muscle. The lumen of the popliteal artery above this fluctuant mass was completely occluded by firm rubbery clot, sections of which could be broken off through the arterial walls by compression. This fluctuant mass extended downward for about 11 cm. and measured approximately 7 cm. in diameter. An attempt was made to dissect this mass away in its entirety but along the medial aspects of the fibula the walls of the sac were inadvertently ruptured, revealing the presence of a huge clot. Subsequent dissection revealed the inner aspect of this mass to be filled by a huge organized blood clot, some of which appeared to be recent in origin but in other areas was organized and contained strands of white fibrinous tissue. This aneurysm seemed to be composed of thinned-out arterial wall surrounding clot, muscle, tendon and fascia. Microscopic examination added nothing to the gross description.

Comment. A diagnosis of bacterial endocarditis was made on a patient presenting with hemiplegia, septicemia and valvular heart disease, although many blood cultures were sterile. During treatment with antibiotics he developed an arterial embolism to the popliteal artery. The immediate complication of thrombophlebitis was not treated with anticoagulants because of the presumptive diagnosis of a septic cerebral embolism. Toward the end of his treatment a ruptured popliteal mycotic aneurysm appeared for which surgery was recommended and refused. Ten days later the patient was admitted in a terminal state with further dissection of the aneurysm.

At autopsy the diagnosis of bacterial endocarditis and ruptured aneurysm was confirmed but the cause of death could not be established.

Case II. G. M. H. D46986 (January 27 to April 13, 1951). A forty-five year old colored male laborer was admitted to the hospital in a semicomatose state with a four-week history of progressive weakness. Twelve hours prior to admission he suddenly became lethargic, developed a right hemiparesis and lapsed into semicoma.

Physical examination revealed a well developed, well nourished, colored male in a drowsy, lethargic state. Blood pressure was 165/0, pulse 106, temperature 100.2°F. and respiration 16. There was a petechial hemorrhage in the left conjunctival sac and right buccal mucosa. There was ptosis of the right lid and the right pupil was larger than the left. He had a stiff neck and positive Kernig and Brudzinski signs. A palpable thrill was felt over the right carotid artery. The heart was enlarged, the first sound was snapping and there was normal sinus rhythm. A grade 4 blowing aortic diastolic murmur was heard best in the third left intercostal space. There were grade 2 aortic and mitral systolic murmurs. A third heart sound was audible at the base. Peripheral signs of aortic insufficiency were present. Neurologic examination revealed a right facial paresis, absent gag reflex and deviation of the uvula to the right. There was a right hemiparesis with a Hoffmann's reflex. The deep tendon reflexes were hypoactive and dysphagia, dysarthria and aphasia were present.

Admission laboratory studies showed hematocrit 45 mm., hemoglobin 13.5 gm., sedimentation rate 28 mm./hr. (Wintrobe), white blood cells 7,800, polymorphonuclears 58, lymphocytes 35, monocytes 3, eosinophils 2, bands 2, icterus index 7.5 units. Urine examination was normal except for 0 to 3 red blood cells, 5 to 10 white blood cells per high power field. Blood sugar was 105 mg. per cent, blood urea nitrogen 11 mg. per cent. An electrocardiogram revealed sinus tachycardia. Spinal tap: pink cloudy fluid, pressure 220 mm. water with normal pulsations, sugar 40 mg. per cent, protein 100 mg. per cent, 2,665 red blood cells/mm.^{3}, 56 white blood cells/mm.^{3}, 100 per cent lymphocytes. Kahn test was negative. A portable chest film revealed clear lung fields, some widening of the aorta and the transverse diameter of the heart was increased.

After the admission studies were completed, nine blood cultures, a urine culture, spinal fluid culture and bone marrow culture were obtained and grown under aerobic and anerobic conditions. A sickle cell preparation was negative in twenty-four hours. For the first four days the patient's temperature averaged 100° to 100.5°F. rectally without chills or signs of toxemia. He was treated supportively with intravenous fluids and bedrest. The neurology consultants believed that the patient had (1) embolism of the left middle cerebral artery, (2) intracerebral hemorrhage. Repeat lumbar puncture revealed a decrease in the number of

red cells to 450/mm.^{3} with numerous crenated cells.

Four days after admission the patient was noted to have a pulsating 4 to 5 cm. mass in the region of the left ulnar artery just below the anticubital fossa. A systolic and diastolic murmur was present over this area which disappeared with compression of the mass. No Branham's sign or change in blood pressure was noted. Over the next twelve hours the mass increased in size and the diagnosis of ruptured mycotic aneurysm of the ulnar artery was made and in spite of the negative blood cultures the patient was started on a regimen of 1.0 million units of aqueous crystalline penicillin every three hours. It was now believed that the presumptive diagnosis of ruptured cerebral aneurysm complicating subacute bacterial endocarditis rested on firmer ground.

The day after therapy was begun the patient's brother added the following points to the history: (1) "fever" twenty years before admission requiring bedrest for three weeks, (2) two months before admission the patient had a tooth extracted without administration of antibiotics, and (3) two weeks prior to admission he had noticed a sudden sharp pain in the left forearm followed by a "swelling" which subsided in five days.

Six days after admission three of the original blood cultures grew out an alpha hemolytic streptococcus and a weakly hemolytic staphylococcus aureus. The penicillin sensitivities of the organisms were found to be 0.78 units/cc. for the streptococcus and 1.56 units/cc. for the staphylococcus. In view of these findings the dosage of penicillin was increased to 1.0 million units every two hours.

Over the course of the next few days numerous splinter hemorrhages appeared and disappeared. A left brachial arteriogram was done and revealed a lobulated aneurysm of the ulnar artery 3 cm. from its origin. (Fig. 1.) Ten days after admission, because of increasing size of the mass, it was surgically excised. Pathologic report revealed a blood clot in various stages of organization and necrosis of the wall of the vessel compatible with a mycotic aneurysm. The remaining course was uneventful. The penicillin dosage was kept at 1.0 million units every two hours for three weeks, maintaining a blood level of 16.0 units/cc. This was then reduced to 1.0 million units every three hours for three weeks, maintaining a level of 8.0 units/cc. For the last two weeks this was reduced to 1.0 million units every four hours, the level being 4.0 units/cc. There was a gradual improvement in the neurologic findings and while under therapy the carious teeth were extracted and physiotherapy begun. All blood cultures taken during and after therapy were negative. During the sixth week of therapy a presystolic mitral murmur was noted to be present and fluoroscopy with barium swallow revealed left auricular enlargement.

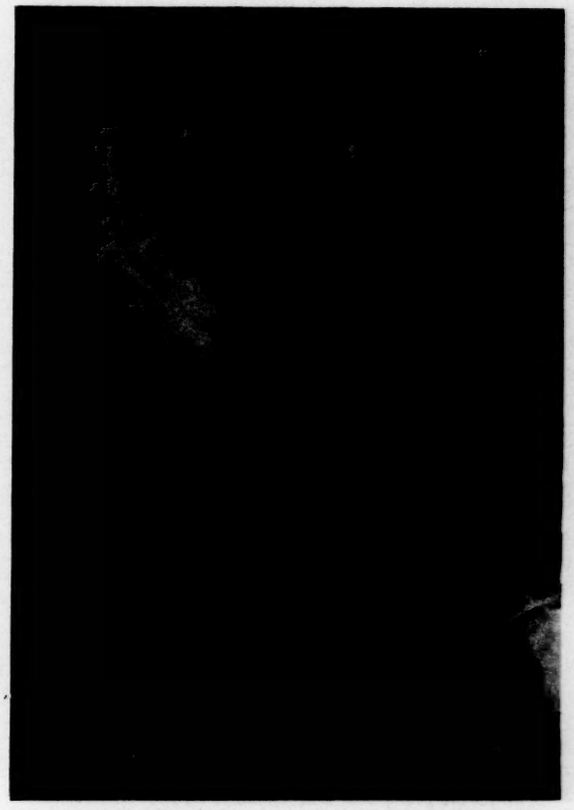

FIG. 1. Arteriogram demonstrating the lobulated false aneurysm which developed in the ulnar artery of Case II. This was ligated and excised several days later.

The patient was discharged seventy-six days after admission to the Cardiac Clinic receiving ambulatory physiotherapy. Since discharge the patient has been seen in the Cardiac Clinic on six occasions, the last visit being July 15, 1953. His blood pressure has averaged 150/30. There have been no signs of congestive heart failure, arrhythmias or active rheumatic fever. He has shown slow but obvious improvement in his neurologic status.

CASE III. G. U. H. 41720 (April 9 to April 10, 1953). A 19 year old white male was admitted with severe headache and vomiting of

eighteen hours' duration and right-sided clonic tonic convulsions of three hours' duration.

Nine years earlier he had been hospitalized for forty days for acute rheumatic fever. Because of two positive blood cultures he had been treated with penicillin for a two-week period. Symptoms of aortic regurgitation appeared sometime during the following year while he was at complete bedrest. He was completely asymptomatic thereafter until eight months before admission when loss of weight, increasing fatigue and dyspnea on exertion gradually developed. Ten weeks before admission, the patient was put to bed and placed on sulfonamides and aspirin with the diagnosis of acute rheumatic fever. This therapy was continued until a few days before admission.

Physical examination revealed an acutely ill, semicomatose patient with blood pressure 175/0, pulse 100, temperature 97.6°F. rectally, respirations 18 per minute. The pupils were dilated and reacted to light; there was conjugate deviation to the right and blurring of the disc margins. Marked trismus with 2 plus nuchal rigidity and positive Kernig and Brudzinski signs was present. There was marked cardiomegaly with occasional extrasystoles, and a short harsh aortic systolic murmur was heard at the base of the heart. There was a loud blowing aortic diastolic murmur. A soft mitral diastolic rumble was heard at the apex without an opening snap. There were the usual peripheral signs of aortic regurgitation present. Neurologic examination revealed facial weakness, spasticity, hypereflexia and a positive Babinski reflex on the left.

In view of our previous experience the diagnosis on admission was subarachnoid hemorrhage, possibly due to ruptured mycotic aneurysm secondary to rheumatic heart disease with subacute bacterial endocarditis.

Laboratory work on admission revealed hematocrit 32, corrected sedimentation rate 30 mm. per hour (Wintrobe), white blood count 25,000, lymphocytes 9, polymorphonuclears 83, bands 8, total eosinophil 31/mm.^{3} Urinalysis: specific gravity 1.022, pH 4.5, albumin 3 plus, sugar 1 plus, otherwise negative. Serologic tests were negative. Blood sugar was 136 mg. per cent. Lumbar puncture revealed initial pressure of 400 mm., bloody fluid, red blood count 750,000/mm.^{3}, white blood cells 50/mm.^{3} 90 per cent polymorphonuclears, chlorides 123 mEq./L., sugar 109 mg. per cent, protein 460 mg. per cent.

Over the next twenty-eight hours the patient's convulsive seizures were controlled with intravenous barbiturates. Six blood cultures, urine culture and spinal fluid cultures were drawn and an intravenous drip of penicillin was begun (12.0 million units/twenty-four hours). The temperature rose to 103°F. rectally, shortly after admission. Eighteen hours after admission a small petechial hemorrhage was noted in the left conjunctival sac. Repeat lumbar puncture revealed a pressure of 460 mm. of water, bloody spinal fluid, 1.5 million red blood cells/mm.^{3}, and 1,200 white blood cells/mm.^{3}, 97 per cent polymorphonuclears. The patient went rapidly downhill and died twenty-eight hours after admission. Twenty-four hours after death a hemolytic staphylococcus aureus, coagulase-negative, was grown out of one blood culture and one spinal fluid culture. The remainder of the cultures were negative. Autopsy was refused.

Comment. The diagnosis of ruptured cerebral mycotic aneurysm made in this case is presumptive. Whenever a patient with rheumatic valvular heart disease and symptoms of endocarditis presents with grossly bloody spinal fluid, this diagnosis should be strongly considered. In addition, recovery of the same organism from the blood and spinal fluid cultures seems to be strong evidence against one of the usual causes of subarachnoid bleeding. The presence of a coagulase-negative staphylococcus might raise the question of its being a contaminate; however, the same organism was recovered from two different fluids cultured at different times. The bacteriostatic therapy given prior to admission may account for the failure to obtain more than one positive blood culture.

REVIEW OF THE LITERATURE PRIOR TO 1923

In 1923 Stengel and Wolferth compiled a list of 217 cases of mycotic aneurysms from the world literature. (Table 1.) Of these 217 cases 187 showed evidences of endocarditis and the remaining cases were presumed to be complications of bacteremia accompanying chronic pyogenic infections, chiefly lung and bone. There were 382 aneurysms in these 217 patients. Multiple aneurysms were commonly found in the smaller vessels of the brain, the aorta and branches of the superior mesenteric and pul-

monary arteries. There were eighty-eight mycotic aneurysms of the aorta; it is impossible to decide how many of these were due to direct extension or to emboli. Involvement of other vessels occurred as follows: intra-abdominal sixty-three, extremities fifty-eight, intracranial forty-two.

TABLE I
DISTRIBUTION OF MYCOTIC ANEURYSMS OF INTRAVASCULAR ORIGIN REPORTED IN 1923[1]

Artery Involved	No. of Cases	No. of Aneurysms
Aorta	66	88
Innominate	2	2
Vertebral	1	1
Basilar	4	4
Internal carotid	3	3
Anterior cerebral and main branches	3	3
Middle cerebral and main branches	14	23
Posterior cerebral	1	1
Posterior communicans	2	2
Small unspecified intracranial	14	49*
Subclavian	1	1
Axillary	3	3
Brachial	10	10
Radial	5	5
Ulnar	5	5
Common iliac	7	7
External iliac	2	2
Internal iliac	1	2
Gluteal	3	3
Femoral	16	17
Profunda femoris	2	2
Popliteal	5	5
Posterior tibial	8	8
Coronary	9	22
Superior mesenteric and branches	24	38
Splenic and branches	15	15
Renal and branches	5	5
Hepatic and branches	19.	19
Pulmonary	6	6
Pulmonary branches	8	21†
	264	382‡

* Plus (numerous in 2 cases).
† Plus (numerous in 1 case).
‡ Plus (numerous in 3 cases)

In order of frequency, the organisms found were streptococci (chiefly non-hemolytic), staphylococci, pneumococcic, influenza bacillus (three times) and gonococcus (once). The following points were emphasized: (1) mycotic aneurysms are more common under the age of forty, (2) are more frequently encountered at arterial bifurcations, and wherever the vessel suddenly narrows or takes a sharp turn, (3) intracranial aneurysms tend to be very small and are easily missed, (4) if necrosis is extensive, perforation may occur before the aneurysm develops, (5) when a mycotic aneurysm of the brain, abdominal cavity or arch of the aorta ruptures, free bleeding is more likely, (6) rupture of a mycotic aneurysm in an extremity produces limited bleeding with the formation of a false sac, (7) aneurysm following embolism was frequently missed, and rupture was frequently confused with phlebitis and (8) expansile pulsation was frequently present even in ruptured aneurysms.

TABLES II AND III
REVIEW OF SIXTY-TWO CASES OF MYCOTIC ANEURYSM REPORTED SINCE 1923

Race: 40 white, 7 colored, 15 unspecified
Sex: 33 male, 21 female, 8 unspecified
Age: youngest 8, oldest 50, 10 unspecified; mean age 26.2 years

TABLE II
AGE BY DECADES

Years	No.
0–10	5
11–20	11
21–30	16
31–40	15
41–50	7
Unspecified	8

TABLE III
CARDIAC DIAGNOSIS

	No.
Rheumatic	36
Congenital	6
Normal	5
Probably normal	1
Unknown	14

REVIEW OF THE ENGLISH LITERATURE SINCE 1923

We have collected fifty-nine cases of embolic mycotic aneurysms from the English literature since 1923 and are adding the three cases of our own already described.

TABLE IV
CASES OF MYCOTIC ANEURYSM COMPLICATING BACTERIAL ENDOCARDITIS ENGRAFTED UPON APPARENTLY NORMAL HEARTS

Age	Valve Involved	Organism	Location of Aneurysm
10[2]	Mitral	Pneumococcus	Abdominal aorta
10[3]	Mitral	Pneumococcus	Descending arch of aorta
28[4]	Aortic, mitral	Pneumococcus	Popliteal and posterior tibial
29[3]	Aortic	Gonococcus	Descending arch of aorta
35[5]	Aortic	Pneumococcus	Hepatic artery
50[6]	Mitral	Friedländer's pneumobacillus	Right middle cerebral

Race, Sex and Age. There were forty white, seven colored and fifteen patients in whom race was not specified. There were thirty-three males, twenty-one females and in eight the sex was not specified. Table II gives the age by decades, confirming Stengel and Wolferth's findings that most mycotic aneurysms occur before the age of

forty. The youngest patient was eight years, the oldest fifty and in eight cases the age was not specified. The mean age was 26.2 years.

Cardiac Diagnosis. In Table III the incidence of the various etiologies is tabulated. As was expected, rheumatic heart disease was the most common cardiac diagnosis. The other groups are too small to be significant statistically.

In Table IV are listed the data on mycotic aneurysms complicating bacterial endocarditis engrafted on normal hearts. It is interesting to point out that in four of the six cases the pneumococcus was responsible.

Table V contains the data on mycotic aneurysms engrafted on congenital heart disease. In this group there was one case of multiple pulmonary artery aneurysms occurring in a patient with patent ductus arteriosus and endocarditis involving the pulmonic valve.

There are fourteen cases included in Table VI in whom the case reports were incomplete. It is probable that many of these were rheumatic in origin. In this group are found two other cases of right sided endocarditis with aneurysms of the ductus arteriosus and branches of the pulmonary arteries.

TABLE V

CASES OF MYCOTIC ANEURYSM COMPLICATING BACTERIAL ENDOCARDITIS ENGRAFTED UPON CONGENITAL HEART DISEASE

Age	Cardiac Diagnosis	Site Involved	Organism	Location of Aneurysm
9[7]	Congenital heart disease	Mitral and tricuspid valve	? diphtheroids	(Subarachnoid hemorrhage)
10[8]	Congenital heart disease	Mitral valve	B. influenza	Femoral and cerebral arteries
16[9]	Coarctation of the aorta and patent ductus	Ruptured aortic cusp	Alpha hemolytic streptococcus	Superior mesenteric artery
29[10]	Subaortic stenosis	Aortic and subaortic area	Unknown	Descending arch of the aorta
41[11]	Interventricular septal defect	Septum	Alpha hemolytic streptococcus	Right middle cerebral artery
44[12]	Patent ductus arteriosus	Pulmonic valve	Streptococcus viridans	Multiple pulmonary arterial aneurysms

TABLE VI

CASES OF MYCOTIC ANEURYSM COMPLICATING BACTERIAL ENDOCARDITIS ENGRAFTED UPON UNSPECIFIED HEART DISEASE

Age	Site Involved	Organism	Location of Aneurysm
10	Mitral valve	Pneumococcus	Abdominal aorta and right cerebral arteries[2]
13	Tricuspid valve	S. viridans	Patent ductus arteriosus[13]
15		S. viridans	Hepatic artery[13]
35	Aortic valve	Pneumococcus	Hepatic artery[5]
39	Mitral valve		Cerebral artery[14]
43	Mitral valve	Streptococcus	Cerebral aneurysm with rupture[39]
	Aortic valve		Cerebral artery with rupture[14]
		S. viridans	Ulnar artery[15]
		Gonococcus	Superior mesenteric[13]
		S. viridans	Left femoral and right common iliac[13]
		S. viridans	Superior mesenteric[13]
		S. viridans	Basilar artery[13]
		S. viridans	Popliteal[12]
	Pulmonary valve	S. viridans	Deep branches of pulmonary artery[13]

Rheumatic Heart Disease. Table VII comprises the data on thirty-six cases with forty-two mycotic aneurysms complicating bacterial endocarditis engrafted on rheumatic heart disease. The ages ranged from eight to forty-five years, with an average age of 28.3. There were thirteen females (white eleven and two unspecified) and twenty-three males (white sixteen, colored three and four unspecified). The causative organism was streptococcus viridans twenty-four, streptococcus salavarius two, hemolytic streptococcus one, staphylococcus aureus one and in eight cases no blood cultures were reported. The aortic valve was involved in eight cases, mitral thirteen, aortic and mitral valve combined thirteen, aortic, mitral and tricuspid valve one, and in one case the valve involved was not specified. In this group of thirty-four cases only seven survived both their endocarditis and the development of a mycotic aneurysm.

The combined data in this series of sixty-two cases with sixty-nine aneurysms are presented in Table VIII. These data may be summarized as follows: (1) Vessels of the head and neck were involved seventeen times. All were intracranial, except one case involving the external carotid.

(2) Upper abdominal vessels were involved twenty-four times, involvement of the superior mesenteric artery or its branches accounting for over one-half of the cases. The remainder were distributed among the abdominal aorta, hepatic, iliac and gluteal arteries. (3) The upper extremities were involved five times and the lower fifteen. (4) In the thorax the aorta was involved four times and the pulmonary artery twice. The latter includes a case of congenital heart disease with a patent ductus arteriosus, and a case of tricuspid endocarditis. In addition, there was one case of endocarditis of the pulmonary valve with a mycotic aneurysm of the ductus arteriosus.

Thirty-three of the sixty-nine aneurysms ruptured; only five patients survived this complication. It is interesting that only five patients with unruptured aneurysms survived. Surgery was performed six times. In the unruptured group, four were ligated and surgically excised and one was simply ligated. These were all peripheral aneurysms except one case involving the superior mesenteric artery. In the ruptured group, ligation and excision of an ulnar artery aneurysm was performed (Case II).

The cases in this study fall into four general clinical syndromes:

1. *Intracranial Syndromes.* There were seventeen such cases fourteen of which presented with a picture of subarachnoid hemorrhage; nine patients were in coma. Ten patients presented either hemiparesis or hemiplegia but only one patient was in shock. Of the eight patients who were not comatose seven had variable but significant headache as one of the presenting symptoms. It is interesting to note that four of the patients in this group lived without any definitive surgical treatment. In three instances the aneurysm was unruptured with no characteristic symptoms or signs. Cerebral embolism was the usual clinical diagnosis but the aneurysm was an unsuspected postmortem finding.

It is therefore suggested that when a patient with valvular heart disease and endocarditis presents with a picture of subarachnoid hemorrhage with or without localizing signs, a diagnosis of ruptured intracranial embolic mycotic aneurysm can be made. The value of carotid angiography in diagnosis remains to be determined.

2. *Abdominal Syndromes.* There were twenty-five cases in this group but data for clinical evaluation are available only in twenty-one. Abdominal pain was prominent in eighteen and one patient presented with a painless pulsatile abdominal mass. Only five of the group had a pulsatile mass with thrill and/or bruit. The picture of an acute condition in the abdomen was seen only in the superior mesenteric group, in which shock was a clinically significant finding and fatal in three. Bloody diarrhea occurred in two cases.

TABLE VII

CASES OF MYCOTIC ANEURYSM COMPLICATING BACTERIAL ENDOCARDITIS ENGRAFTED UPON RHEUMATIC HEART DISEASE

(36 cases, 42 aneurysms)

Age	Valve Involved	Organism	Arterial Site of Aneurysm
8	M,A,T	S. viridans	Left posterior tibial and left middle cerebral[16]
15	M		Right hemisphere[17]
16	M	Streptococcus	Superior mesenteric[18]
17		S. viridans	Superior mesenteric[15]
17	M,A	S. viridans	Descending aorta[19]
18	M		Common iliac[20]
18	M	S. viridans	Basilar[15]
20	M	S. viridans	External carotid[21]
20	M	Staphylococcus	Cerebral*
20	M		Left brachial artery[22]
21	M	S. viridans	Left popliteal and left external iliac[23]
22	A	S. viridans	Right gluteal[23]
22	A	S. viridans	Right ulnar[24]
22	M	S. viridans	Cerebral[25]
23	A	S. viridans	Right axillary and cerebral[26]
24	M,A	S. viridans	Right gluteal[27]
25	A	S. viridans	Superior mesenteric[28]
26	M	S. viridans	Superior mesenteric[29]
27	M	S. viridans	Superior mesenteric[30]
28	A		Right popliteal and cerebral†
28	M,A	S. viridans	Basilar[31]
34	M	S. viridans	Left common iliac[32]
34	M,A	S. viridans	Right iliac and superior mesenteric[33]
35	M,A	S. viridans	Right femoral[34]
36	M	S. hemolyticus	Superior mesenteric[28]
38	M,A		Superior mesenteric[35]
38	M,A	S. viridans	Superior mesenteric[18]
38	M,A		Superior mesenteric[28]
39	M	S. salivarius	Right posterior tibial[35]
39	M,A	S. salivarius	Posterior tibial[35]
39	M	S. viridans	Right femoral[33]
40	A		Left femoral[36]
40	A	S. viridans	Left posterior tibial[37]
41	M,A	S. viridans	Superior mesenteric[18]
45	M,A	S. viridans	Cerebral and left ulnar‡
50	A	S. viridans	Cerebral[38]

* Case III.
† Case I.
‡ Case II.

In this group patients present the picture of an acute surgical condition of the abdomen or a pulsating abdominal mass. Abdominal pain may be present in both. Abdominal pain occurring in a patient with endocarditis is often considered to represent an episode of recent embolization. It must be emphasized that such an episode may represent rupture of a previously unsuspected mycotic aneurysm. Careful evaluation may lead to successful surgical intervention.

When a pulsating intra-abdominal mass develops, the diagnosis is relatively easy and surgi-

cal exploration should always be considered. Ligation and excision should be performed unless an important vessel is compromised, when excision with a vessel graft seems more logical.

3. *Thoracic Syndromes.* The descending aorta was involved four times. In three the symptoms were severe chest pain and sudden death, one rupturing into the esophagus and another into the left hemithorax. In the fourth patient the aneurysm was a surprise postmortem finding in a patient who had complained of substernal discomfort. The aortic valve was involved twice, the mitral once and the fourth was unspecified.

These patients present with severe chest pain, intractable shock and death. This is usually a dramatic terminal event. Prior to rupture the symptoms arise from compression or displacement of contiguous structures.

There were two cases of aneurysms of the pulmonary artery, one secondary to pulmonic valve involvement; in the other there was endarteritis of the patent ductus as well as pulmonic valve endocarditis. In both the aneurysms were surprise postmortem findings although one had had hemoptysis for several weeks.

4. *Extremity Syndromes.* In contrast to the free, unrestricted bleeding of ruptured mycotic aneurysms of the thorax or abdomen, bleeding into the extremities is usually limited by fascial planes and presents a clinical picture that can be recognized.

In eighteen of the twenty cases in the present series a mass ultimately presented. Pain was present in fourteen and considerable confusion often arose because of the delay that occurred from the time of this presenting symptom and the eventual development of an expansile mass. The sudden development of the mass was due to rupture of an unsuspected mycotic aneurysm. The presence or absence of a thrill or bruit was of no value in establishing whether or not the aneurysm had ruptured. Ruptured aneurysms may continue to present thrills and bruits and the pulse need not be diminished or absent below the site of rupture. Ten had edema associated with the pain and the clinical picture may be confused for several days with thrombophlebitis. There may be compression of nerves with development of peripheral neuritis (two cases).

The diagnosis of mycotic aneurysm usually depended upon the development of pain and a mass with or without pulsations. This is a serious complication and usually demands surgical intervention, preferably ligation and excision with arterial graft if necessary.

TABLE VIII

INCIDENCE OF VESSEL INVOLVEMENT IN SIXTY-TWO CASES WITH SIXTY-NINE ANEURYSMS

Vessel	No.	Rupture	Remarks
"Cerebral"	10	8	Multiple;[39] four of ruptured lived[11,17,25] *
Middle cerebral	3	3	
Basilar	3	1	
External carotid	1	..	
Right axillary	1	..	
Brachial	1	..	Successful excision[22]
Ulnar	3	1	Successful excision of ruptured case *
Descending aorta	4	3	
Abdominal aorta	1	1	
Iliacs	5	..	
Femorals	6	2	1 Unruptured excised;[34] 1 unruptured ligated[20]
Gluteal	3	2	
Popliteals	4	1	1 Unruptured, surgically excised—later amputation of foot for gangrene[4]
Posterior tibials	5	4	
Pulmonary	2	..	Right-sided endocarditis with multiple pulmonary artery aneurysms[12,13]
Ductus arteriosus	1	..	Right-sided endocarditis with multiple pulmonary artery aneurysms[13]
Superior mesenteric	14	6	Successful removal of an unruptured aneurysm;[30] 1 explored without definitive surgery[9]
Hepatic	2	1	
	69	33	

* Case II.

SUMMARY

1. Two illustrative proven cases and one probable case of embolic mycotic aneurysm complicating bacterial endocarditis are presented.

2. Fifty-nine additional cases reported since the last complete review in 1923 have been compiled and are analyzed.

3. The development of an embolic mycotic aneurysm is an unusual but serious complication of bacterial endocarditis.

4. Four characteristic clinical syndromes are described which allow for recognition or a high index of suspicion. These syndromes reflect the intracranial, abdominal, thoracic or peripheral extremity location of the mycotic aneurysm.

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Seminars on Liver Disease

Physiology of the Liver*

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BEFORE discussing the physiology of the liver a few of the salient structural features must be emphasized. This will make for clarity in evaluating the role played by the liver in the various activities of the body.

The liver is the largest gland in the body. It weighs about 1.5 kg. and makes up about 3.3 per cent of the total body weight.

ORIGIN OF THE LIVER

Embryologically the liver develops as an evagination of the primitive foregut (duodenum) in the form of a compound tubular gland. This gland invades the mesentery, splits it and becomes encapsulated by it in the region of the septum transversum (diaphragm). Hepatic parenchymal cell cords proliferate and extend in between the umbilical and vitelline veins. This causes the veins to form a solid labyrinth of sinusoids whose endothelial walls are separated by a potential space from the outer borders of the cords of hepatic parenchymal cells. Under certain pathologic conditions this space can be filled with fluid derived from the blood or from the hepatic parenchyma.

STRUCTURE OF THE LIVER

The cells of the liver are highly specialized both functionally and morphologically. They are polygonal and usually have one nucleus but the presence of two nuclei in an hepatic parenchymal cell is not uncommon. Aggregates of parenchymal cells constitute the lobules. The liver is made up of hundreds of thousands of lobules which should be considered as its architectural units. A lobule is a group of hepatic parenchymal cell cords, radially arranged like the spokes of a wheel, with a central vein draining the blood into the sublobular branches of the hepatic vein. Running as a lumen between two adjacent cell cords are the intralobular bile capillaries which, after joining the intralobular bile passages, drain into the interlobular bile ducts. The blood sinusoids traversing the lobules are separated from one another by two cords of hepatic parenchymal cells, with a bile capillary between them. No definite lymph vessels have been demonstrated in the lobules; however, lymphatic vessels are present in the interlobular spaces. Elias[1] recently presented a new concept regarding the structural pattern of the liver. This will be referred to when blood supply is discussed.

By special staining methods the presence of glycogen and fat in the hepatic cells can be easily demonstrated. Under certain conditions the quantity of fat or of glycogen in the liver can be made to increase or decrease.

The Kupffer cells found in, or in close association with, the walls of the sinusoids are the reticuloendothelial cells of the liver. They are phagocytic and form an important part of the reticuloendothelial system.

BLOOD SUPPLY OF THE NORMAL LIVER

The hepatic lobule is the histologic unit of the liver. The functional unit probably consists of two cords of hepatic cells, with an enclosed sinusoid on one side and a bile capillary on the other. Elias[2–6] suggested the concept of an hepatic lamina, which is the thickness of one cell and is perforated at frequent intervals to permit the passage of sinusoids. He expressed the belief that the hepatic lacunas[1] form a labyrinth. He would substitute his concept for the conventional idea of the cord that consists of a double row of hepatic cells. The classic histologists believed that cylinders of hepatic cells were surrounded by blood but recent observations have demonstrated that blood-filled sinusoids are cylinders of blood cells surrounded by hepatic parenchyma. However, in consideration of the hepatic circulation, the liver can be divided into two or more entities that have a distinct vascular supply.[7] The vascular system of the liver in higher species is unique in that the hepatic

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blood is received from two separate sources,[8] the portal vein and the hepatic artery.

Portal Venous Blood Supply. The portal venous system drains most of the blood from the gastrointestinal tract, spleen and pancreas. The splanchnic region, which is supplied by large arteries that possess extensive capillary beds and a highly developed system of vasomotor control, comprises the vast vascular bed of the portal system. Vasomotor nerves and smooth muscle fibers have been found in abundance in the portal vein and its tributaries. The portal vein, interposed between the hepatic capillaries (sinusoids) and the capillary bed of the digestive tract and other abdominal viscera, carries to the liver blood that is enriched with freshly absorbed nutritive materials.

It is important to keep in mind that portal blood is the carrier of most of the food brought to the liver. The importance of passage to the liver of absorbed products of digestion first becomes apparent when the functions of the liver are considered. During digestion, and with increase in bodily metabolic processes, the flow of blood in the portal system is greatly increased. Recent work has demonstrated that portal venous pressure is greater than pressure in other veins of the body but that it is low when compared with arterial pressure. Grindlay and associates[9] found that the mean pressures in the hepatic veins of normal dogs were 2.1 cm. of isotonic saline solution, 7.2 cm. in the portal vein and 1.8 cm. in the abdominal vena cava. Pressure in the portal veins of dogs that had cirrhosis of the liver, or had the portal veins occluded, was approximately twice normal.

Conclusive evidence exists that the flow of blood in the portal system of veins is streamlined. When India ink is injected into the superior mesenteric vein, particles of ink are found only in the right lobe of the liver; when ink is injected into the splenic vein, particles are found only in the left lobe.[10] Furthermore, transillumination and direct observation of the flow in the portal vein after injections of dye[11,12] yields similar conclusions. It is therefore generally agreed that the flow of blood in the portal vein is laminar and that distribution of portal blood in the liver is selective. Blood from the upper part of the gastrointestinal tract, from parts of the colon and from the spleen goes to the left portion of the liver whereas the remainder of the portal blood goes to the right. Localization of abscesses in the liver may result from such laminar flow.

The question has been raised as to whether portal blood is essential for the liver. The Eck fistula,[13] which will be described later, has provided an excellent experimental procedure by which the influence on the liver of loss of the portal venous circulation could be investigated. It has been observed repeatedly in animals that loss of portal blood produces hepatic atrophy and deranges hepatic structure and function.[14–15] Hepatic tissues become flabby; the liver is reduced to half its normal size or less, and it becomes pale, mottled and yellow. The central portions of the lobules undergo atrophy and become loaded with fat. The animal loses weight but the proportional loss of weight of the liver is far greater than is the loss in body weight.[15–16]

A reverse Eck fistula, which also will be described, produces increase in flow of blood to the liver and increase in size of the organ.[17]

Results obtained from various experiments performed by Mann and others[16] emphasize the importance of the portal circulation in restoration of the liver after partial hepatectomy. It was observed that the presence of portal circulation may be as important in the causation of hepatic hypertrophy as is the absence of portal circulation in the production of hepatic atrophy.

Hepatic Arterial Blood Supply. The hepatic artery is not large but the pressure in it is the same as that in any systemic artery of its size; namely, about 120 mm. of mercury. The hepatic artery carries a small volume of blood at great velocity and with great pressure, while the portal vein carries a large volume of blood slowly and with much less pressure. The question is still unsettled as to whether the liver can survive the loss of its supply of arterial blood. Death has occurred after ligation of the hepatic artery.[18–19] Mann[19] reported that in the dog ligation of the hepatic artery at its point of origin is without effect but that ligation of the hepatic branch of the hepatic artery at its entrance into the liver always is followed by death; the rat, however, survives such a procedure. It must be remembered that in the rat small collateral arteries pass to the liver from several sources. Infarction and widespread necrosis occur on elimination of the entire arterial supply to the liver.

Grindlay, Mann and Bollman[20] in a report of a more recent study on the effect of occlusion of the supply of arterial blood to the normal liver stated that the arterial supply presumably was re-established by collateral vessels (1) in the diaphragmatic ligaments, (2) on the surface of

the common bile duct, (3) in the wall of the vena cava below the diaphragm and (4) possibly in adhesions that bind the liver and neighboring organs. Markowitz and associates[21] suggested that the immediate lifesaving function of the hepatic artery in the dog is to maintain the oxygen tension at a value that is incompatible with proliferation of the anaerobic organisms that are constantly present in hepatic tissue. The blood in the portal vein carries some oxygen but most of the oxygen that reaches the liver is carried by the hepatic arterial blood, which provides about 25 per cent of the total supply of blood to the liver.

Intrahepatic Circulation. The liver is provided with two sources of blood, and the blood coming from these two sources leaves the liver by way of a common channel, the hepatic veins. At some site in the hepatic substance the portal and arterial blood must meet and mix before drainage into the hepatic veins has occurred. Use of the technic of transillumination by Mann and me,[8,22,23] and by Knisely,[24] provided a means for direct observation of the intrahepatic circulation *in vivo*, under various magnifications, for detailed long-continued study of the various components of the vascular bed within the liver.

Mann and I noticed that the surface of the mammalian liver, as seen with low-power magnification, presented numerous fairly definite, irregularly polygonal areas corresponding to lobules, each of which was drained by a central vein; the peripheries, however, were ill defined and merged with the borders of neighboring units of similar shape and structure. Compared with the liver of the frog, mammalian liver presented far more definite lobules in each of which the draining vein was centrally located. We were impressed by the relatively great number of sinusoids that emptied into the central veins and also by the more clearly seen ramifications of the other receiving veins noted under low-power magnification.

The branches of the hepatic artery and the portal and hepatic veins could not be distinguished clearly under extremely low-power magnification but it could be seen that they and their ramifying sinusoids had an arborescent distribution throughout the hepatic substance. However, when greater magnifications were used, the portal vein and hepatic artery, which under low-power magnification had been disguised by their interlobular sheaths, and appeared only as reddish strands, were seen more clearly in the periphery of the lobule and could be observed to empty into the sinusoids that ramified in a radial manner between columns of parenchymatous cells. Long ramifications of the hepatic vein were commonly located in the border of the liver; these ramifications received the sinusoids of that region and coursed parallel to the most peripheral edge of the liver to join the neighboring veins. The portal branches and corresponding ramifications of the hepatic artery frequently occupied such positions in the border of the liver and supplied the sinusoids of the region with both arterial and portal blood.

Intermittence of Circulatory Activity. General survey of an illuminated lobe reveals that the circulatory activity in different regions of the liver is highly variable; this is noted even in individual sinusoids of a single lobule. In one lobule every sinusoid may be open and blood courses through the lobule toward the central vein; in another, only a few sinusoids may be patent while the majority are inactive. Some of these inactive sinusoids contain a large number of blood cells lying motionless in their lumina; others contain a few scattered, motionless cells and still others appear to be contracted and to contain no blood cells. Intermediary stages of all degrees of circulatory activity can be observed in the various lobules.

In the course of a few hours Mann and I[23] noticed intermittency of circulatory activity in any group of lobules. This intermittency was subject to variation. The whole circulatory condition of a single lobule, or of several adjacent lobules, could change from inactivity to partial activity and finally to full activity. In the phase of full activity every sinusoid and even the oblique and transverse connections between sinusoids opened and blood flowed rapidly through the lobule into the central vein. These alterations in circulatory activity were not regular in occurrence nor did they take place in uniform sequence. An inactive portion of a lobule frequently remained in one state while a neighboring portion of the same lobule made two or three shifts from inactivity into various degrees of activity and again returned to a state of inactivity.

These shifts in activity took place much more frequently in mammalian than in amphibian (frog) liver. In addition, the regions of inactive sinusoids were more extensive but less numerous in the liver of the frog than in that of the rat. Regions where inactive sinusoids were filled with

motionless corpuscles were found throughout the lobe, interspersed among regions where the lumina of inactive sinusoids contained relatively few corpuscles. When sinusoids of either type resumed activity, it became impossible to distinguish one from the other on the basis of the number of blood cells transported through it. It can be stated with assurance that among animals of the same age, under identical conditions, more than 75 per cent of the regions studied displayed inactivity when neither excitatory nor inhibitory factors were in operation over the intact liver.

One type of intermittence observed in the mammalian liver is in the rate of flow through sinusoids. When a region was watched for an hour or more, it was observed that for several minutes the blood in one set of sinusoids coursed rapidly, then gradually slowed for a while, only to increase again. In two or more adjacent regions these changes in rate of flow occurred asynchronously and the shifts in rate in different groups of sinusoids exhibited no regularity or sequence.

Distribution of Venous and Arterial Blood. At the ill defined borders of a lobule, branches of the hepatic artery and portal vein break up into fine ramifications that usually empty independently into the sinusoids. The most frequently observed phenomenon is branching of the portal vein into several sinusoids as it traverses the interlobular region, together with its final termination in a number of sinusoids that drain centrally into the adjacent lobules. The corresponding arterial branches that accompany those of the portal vein in the interlobular margins are more difficult to observe because of their smaller caliber and less distinct color. However, it soon is evident that the blood flowing intermittently in the fine arterioles also empties directly into several sinusoids that start in the periphery of the lobule and course centrally in the same manner as those supplied by the portal venules.

Occasionally, two branches of the hepatic artery rather than one accompany the portal vein, one on either side in the interlobular space; these supply sinusoids of the two adjacent lobules. In the peripheral and intermediate zones of the lobules, sinusoids of the portal vein frequently communicate, by means of short, oblique or transverse sinusoids, with those that carry arterial blood. Both sets of sinusoids drain into the central vein and, in the region of the central vein, no distinction can be made between the portal and arterial sinusoids. In the periphery of the lobule the flow in arterial sinusoids is much faster than that in the portal sinusoids.

A whole sector of a lobule frequently is supplied independently by either purely arterial or purely portal blood. In regions where both the supplying (portal or arterial) and the draining (hepatic venous) vascular systems of the liver are observed in the same focal plane, they dovetail in such a way that the cords of hepatic parenchymatous cells separate the elements of the two systems by a distance equal to the width of the cord of hepatic cells. However, cross communications are observed at various levels between the neighboring sinusoids.

In addition to the communication between portal and arterial blood within the lobule, two other modes of communication between the two kinds of blood are evident:

1. Direct anastomotic communications are present between corresponding ramifications of the portal vein and the hepatic artery in their interlobular course. (Fig. 1.) However, these anastomoses are not observed as frequently in mammalian as in amphibian livers. Sometimes the arterial ramifications end at the anastomosis in the interlobular branch of the portal vein and no other arterial vessels are seen thereafter; the blood in the portal vein, however, is observed to flow much faster distal to that anastomosis. In other regions transverse connections, like rungs of a ladder, are present between the two vessels as they continue an independent course before they break up into several sinusoids at their terminations. (Fig. 1.)

2. Arterial ramifications end frequently in the terminal branches of the portal vein just before the latter branches empty into the sinusoids at the periphery of the lobules. (Fig. 1.) Thus it is evident that the supply of arterial blood to the hepatic parenchyma is by no means a negligible quantity and it is not justifiable to state that the hepatic artery supplies only the supporting tissue of the liver.

Arteriovenous communications between ramifications of the hepatic artery and of the hepatic vein were not observed in any of the mammalian livers that Mann and I studied.

In general, the sinusoids that drain into the ramifications of the hepatic vein are slightly ampullated just before they join the draining vein and are narrowed at their point of junction with the vein to such an extent that the impression of a sphincter is created. The sinusoids

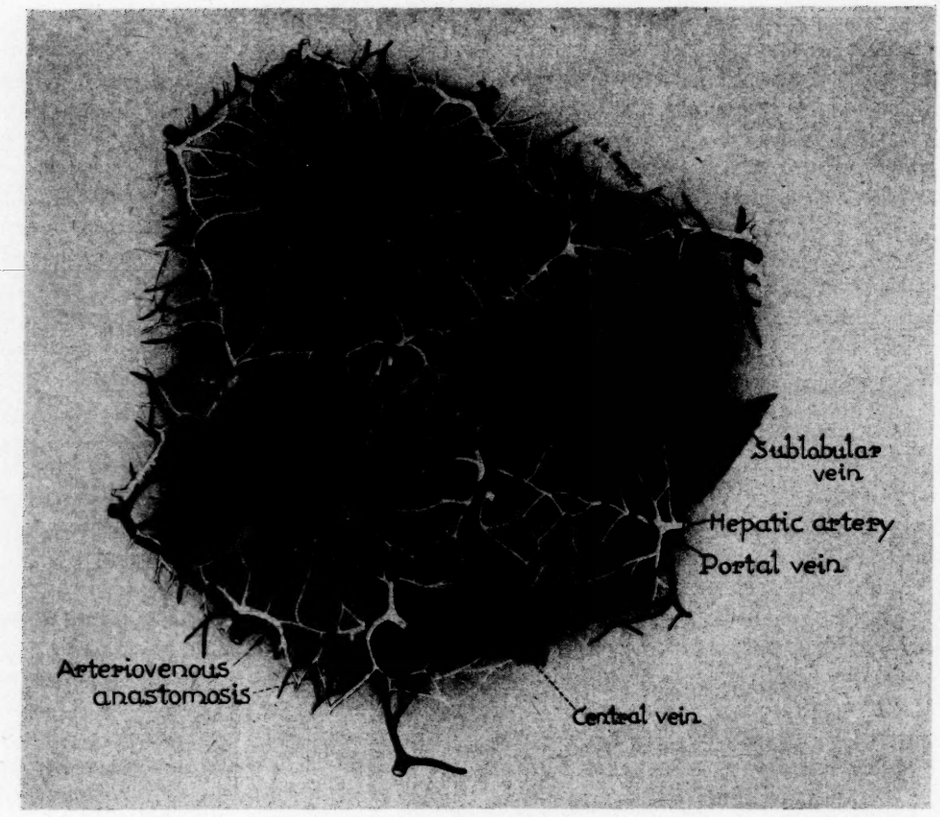

FIG. 1. Distribution and manner of communication of the arterial and venous blood within the mammalian liver. The white vessels are arterial, the black are portal and the shaded are hepatic venous radicles. Note the arteriovenous anastomoses between the arterial and portal radicles in their course through the interlobular spaces. (Reproduced with permission from Wakim, K. G. and Mann, F. C.[8])

supplied by the portal vein and hepatic artery also appear to undergo narrowing at their points of origin from the main vessels but to a much less extent than do those of the tributaries of the hepatic vein.

Daniel and Prichard[25] emphasized the presence of innumerable intrahepatic pathways of various lengths through which blood can pass from the portal vein to the inferior vena cava. They found that the pathways that transmit blood through parenchyma situated at the periphery of the liver are longer than are those by which blood is carried through parenchyma situated in the more central regions of the liver.

Quantity of Blood Flowing Through the Liver. The total quantity of blood that flows through the liver varies within wide limits. Similarly, the relative quantity of the total flow that reaches the liver through either the portal vein or the hepatic artery is also greatly variable. Sometimes a reciprocal response can be noted between the flow of blood from the hepatic artery and from the portal vein into the liver; thus an increase or decrease in flow from one is accompanied by the opposite change in the other. Administration of glucose[26–28] or of isotonic solution of sodium chloride or sucrose causes an increase in flow in both the portal vein and the hepatic artery. Use of bile salts has been reported to produce an increase only in the hepatic arterial flow. The splenic vein provides an amount that varies from 10 to 35 per cent of the total amount of venous blood that flows to the liver.

The total hepatic blood flow was determined in patients by Bradley and associates[29] who inserted catheters into the hepatic veins; they found this flow to average 1,500 cc. per minute, with a range from 1,085 to 1,845 cc. Dock[30] perfused normal human livers obtained at necropsy and reported an average total portal and hepatic flow of 2,420 cc. per minute. Lichtwitz[31]

estimated the total daily flow of blood through the human liver at 2,000 L.; of this total, 1,200 L. are portal and 800 are arterial in origin.

Even though the hepatic artery may contribute only from 12 to 44 per cent of the total flow of blood to the liver, several investigators[32–34] have demonstrated that it supplies an average of 40 per cent, and may supply as much as 62 per cent of the supply of oxygen to the liver. Soskin and co-workers[35] found that the proportion of blood which enters the liver by way of the portal vein or by the hepatic artery may vary as widely as 10 to 90 per cent relative to either vessel. Schwiegk[34] suggested the existence of a mutual relationship between the hepatic artery and portal vein in the normal liver; a decrease in portal flow produced mechanically by means of reduction in caliber of the portal vein led to increase of 50 to 100 per cent in hepatic arterial flow.

LYMPHATICS OF THE LIVER

The lymphatics of the liver and the role of the liver in the formation of lymph have not been studied extensively. Since 1894, when Starling[36] demonstrated an increase in the flow of lymph in the thoracic duct following ligation of the inferior vena cava above the entrance of the hepatic veins, it has generally been presumed that the liver gives origin to the major portion of the lymph present in the thoracic duct. However, Markowitz and Mann[37] reported that after complete hepatectomy the flow of lymph in the thoracic duct was insignificantly reduced. Johnson and Mann[38] noted an intimate association between the lymphatics and other anatomic components of the liver. They found lymph vessels within the walls of the bile ducts.

Cain and others[39–40] studied, in trained dogs, the composition and rate of flow of hepatic lymph after direct cannulation of hepatic lymph vessels. They also compared the values obtained for hepatic lymph with those of lymph from the thoracic duct. The average rate of flow of hepatic lymph was 2.26 cc. per ten minutes as compared with 4.6 cc. per ten minutes from the thoracic duct. They concluded that the liver probably contributed a fourth to a half of the total volume of the lymph delivered by the thoracic duct. The intravenous administration of a 20 per cent solution of glucose produced an increase of approximately 70 per cent in the rate of flow of lymph from both the liver and the thoracic duct.

Food and exercise affected lymphatic flow in the dogs.[39–40] Ingestion of food caused an increase in the rate of flow of lymph from the thoracic duct of about 80 per cent and of that from the liver of 105 per cent. Brief periods of exercise caused a much greater increase in lymph from the thoracic duct than from the liver.

Acute poisoning with carbon tetrachloride led to the production of bloody lymph by the liver but caused no gross change in the volume-flow of lymph. Experimental hepatic cirrhosis produced by exposure of the dogs to carbon tetrachloride vapor over long periods greatly increased the flow of hepatic lymph, and moderately increased the flow of thoracic duct lymph.[39–40] In dogs with experimentally produced venous congestion of the liver, or cirrhosis of the liver, Nix and associates[41] noted that the flow of hepatic lymph was two to five times that obtained from normal livers. They estimated that the equivalent of 70 to 207 per cent of the total circulating plasma proteins passed through the lymphatics of the liver in twenty-four hours.

The protein content of hepatic lymph is five-sixths that of blood plasma, and that of lymph from the thoracic duct is half that of plasma. The sugar and chloride content of lymph from the liver and of lymph from the thoracic duct is slightly higher than that of plasma; the inorganic phosphate is the same in all three, but the concentration of alkaline phosphatase is 30 to 50 per cent lower in lymph from each source than it is in plasma. The prolonged drainage of lymph from the thoracic duct, or from the lymphatics of the liver, leads to hypoproteinemia.

Volwiler, Grindlay and Bollman[42] reported that in experimental ascites associated with venous congestion of the liver the ascitic fluid appears to be derived from hepatic lymph and has a very high protein content. If ascites was caused by inducing hypoproteinemia in dogs with extrahepatic obstruction of the portal vein, the ascitic fluid was a thin, watery transudate with a very low protein content.

NERVE SUPPLY OF THE LIVER

The liver is supplied by sympathetic nerves through the splanchnics and by parasympathetic nerves through the vagus. Stimulation of the sympathetic nerves, or administration of certain sympathomimetic drugs (epinephrine), produces constriction[43] of the blood vessels of the

liver and a rise in blood sugar attributable to the increased liberation of glucose through glycogenolysis. By vasoconstriction and decrease in blood flow through the liver, the sympathetic nerves may cause a reduction in secretion of bile. The hepatic artery and its ramifications are richly supplied with vasomotor nerves. Intravenous injection or local application of epinephrine, or stimulation of the hepatic nerves, causes constriction of the intrahepatic blood vessels.[44] In addition, portal pressure markedly increases and transhepatic circulation becomes accelerated.[43] Stimulation of the vagus nerves produces no perceptible effect on the intrahepatic vessels. Stimulation of the parasympathetic fibers causes an increase in secretion of bile.

METHODS EMPLOYED IN STUDY OF PHYSIOLOGY OF THE LIVER

The difficulties encountered in the development of sound methods for investigation of hepatic physiology constitute the chief reason for the delay in accumulation of reliable information in regard to the role of the liver in the living organism. Some of the several methods employed in study of the liver and the biliary apparatus are:

Biliary Fistula. By production of a biliary fistula information is obtained regarding the quantity and quality of the various constituents of bile. The action of various cholagogues and choleretics, and the mechanism of evacuation of the gallbladder can be studied by this procedure. The importance of the presence of bile in the gastrointestinal tract can be appraised by this method.

Analysis of Blood of the Portal and Hepatic Veins. By use of the London cannula and other aids blood can be collected from the portal vein and from the inferior vena cava above the entrance of the hepatic veins. Data obtained by analysis of blood so obtained give information regarding the changes wrought by the liver on the absorbed products of digestion. Some information on the detoxification function of the liver also can be obtained by such analyses.

Eck Fistula. This is the result of a surgical procedure by which the portal vein and the inferior vena cava are joined in a side-to-side anastomosis. The portal vein is ligated above the anastomosis, before the vein empties into the substance of the liver. This shunts the portal blood into the inferior vena cava without its going through the liver and yields some valuable information on the role of the liver in the intermediary metabolism of absorbed food products. For the reverse Eck fistula the inferior vena cava instead of the portal vein is ligated above the anastomosis but before the entrance of the hepatic veins into the vena cava. This procedure provides for passage through the liver, and through the parietal abdominal wall, of all the blood that drains into the portal vein and inferior vena cava caudad of the hepatic veins. The reverse Eck fistula is used preliminary to hepatectomy in order to supply sufficient collateral circulation for drainage of the blood from the abdominal viscera without the congestion that may occur after hepatectomy.

Perfusion of the Liver. Perfusion experiments have been useful, among other things, in study of the formation of ketone bodies by the liver and also in study of the formation of urea. Glycogenesis and glycogenolysis are other important metabolic processes which have been investigated with the aid of perfusion experiments.

Liver Function Tests. Liver function tests obviously are dependent on physiologic processes. A great variety have been developed to evaluate the status of the liver.

Hepatectomy. Complete extirpation of the liver brought out the important facts that, in the dog, life cannot be maintained longer than about sixty hours after complete hepatectomy and that maintenance of the blood sugar level is chiefly a function of the liver. Incomplete hepatectomy indicated the great regenerative capacity of the liver; 85 to 90 per cent of the liver could be extirpated before any disturbance, as reflected in liver function tests, could be noticed. This is an excellent index of the high functional reserve the liver possesses.

Postmortem Analysis of Hepatic Tissue. This must be done immediately after death. Reliable information regarding the various substances stored in the liver and their concentration can be obtained in this way.

FUNCTIONS OF THE LIVER

From the various kinds of experimental evidence mentioned in the preceding paragraph, and also from clinical observation, it has been learned that the liver plays a major role in the nutrition and maintenance of the body. Some of the important functions of the liver so demonstrated include:

Chologenesis. The liver contributes to the manufacture of bile. It is responsible for the elimination of bile into the biliary apparatus.

Regulation and Maintenance of Blood Sugar Level. This is performed by the formation and storage of glycogen (glycogenesis) and by the breakdown of glycogen to glucose (glycogenolysis) according to body needs. When the diet does not contain carbohydrates, the liver manufactures them from non-carbohydrate sources such as proteins, fats and lactates (gluconeogenesis).

Protein Metabolism. Deamination of amino acids and synthesis of urea are performed chiefly by the liver. The specific dynamic action of foods in general, and of proteins in particular, is attributed to the liver.

Fat Metabolism. Elaboration of unsaturated fatty acids and phosphorylation of fats occur to a large extent in the liver. Some believe that unsaturated fatty acids are selectively retained by the liver.

Formation of Ketone Bodies. There is good evidence that it is chiefly in the liver that ketone bodies are formed from fats, proteins and pyruvate.[45–46]

Formation of Plasma Proteins. Plasma proteins are produced in part by the liver,[47–52] especially fibrinogen and albumin.

Detoxication. The liver plays an important role in protection of the organism from some harmful exogenous or endogenous substances. The liver detoxifies certain substances in one or more the following ways: (1) The substances are destroyed by the liver; for instance, strychnine, procaine, pentobarbital sodium and nicotine are destroyed to a large extent by the liver. (2) The liver makes certain substances innocuous by conjugation; conjugation of indoles with sulfate radicals, of phenol with glucuronic acid and of benzoic acid with glycine occurs in the liver. (3) Certain substances are temporarily held in the liver cells and are released slowly in amounts too small to be injurious to other more vulnerable organs or tissues. (4) The liver may rid the body of certain toxic substances by excreting them with the bile into the intestine where they are eliminated.

Storage of Blood. The liver is one of the important depots for temporary storage of blood. It shares this function with the spleen and other parts of the body.

Storage of Metals. Iron and copper in the body are stored in the liver, among other organs. Some vitamins are stored in the liver and others may be manufactured, from precursors, by the liver.

Formation and Storage of Vitamins. The liver is an excellent metabolic factory, rich in the necessary enzymes and coenzymes. Most of the components of the vitamin B complex exist in the body as parts of coenzymes. Riboflavin is found in large amounts in fresh liver. Fat-soluble vitamins, especially vitamins A and D, also are stored in the liver. The livers of cod and halibut are the richest available natural sources of vitamins A and D. The ability of liver extract to combat pernicious anemia is attributed to its content of cyanocobalamine.[53]

Erythropoiesis and Storage of Antianemia Principle. According to Copenhaver[54] the liver not only stores the erythrocyte-maturing factor but also produces a modification of it which is essential for its production. Whipple and associates stated that the role of the liver in erythropoiesis is not limited only to storage of an erythrocyte-maturing factor but it also plays a significant role in the manufacture of a substance essential for the development of red blood cells. Under normal conditions the antianemia principle is produced by action of the "intrinsic factor" on the extrinsic factor contained in the ingested food. The product, the antianemia principle, is stored in the liver chiefly (possibly in other organs too) and is drawn upon for the normal development of red blood cells in the bone marrow.

In early embryonic life the liver is an important erythropoietic organ. However, in later prenatal life the liver normally loses the function of erythropoiesis. In the presence of very severe and long-lasting anemia, even in adults, the liver may revert to its embryonic function of erythropoiesis.

Coagulation of Blood. The evidence to date suggests that the liver is the chief if not the sole source of fibrinogen, a plasma protein which is essential for the formation of a clot. Prothrombin, another protein compound which is essential in the coagulation process, is produced by normal hepatic parenchyma in the presence of vitamin K. For absorption of the fat-soluble vitamin K the presence of bile salts in the intestine is required; and bile salts are manufactured by the liver. The liver also has a share in the liberation of heparin, an important anticoagulant produced by mast cells. Dicumarol prevents or delays coagulation, depending

on dosage, by inhibiting the manufacture of prothrombin by the liver.

BILE

In order to obtain a thorough understanding of the role of the liver in the manufacture of bile, certain salient anatomic facts pertinent to the biliary apparatus should be discussed.

Relevant Anatomy. The intralobular bile capillaries lie between two adjacent liver cell cords. These join with intralobular bile ducts which empty into interlobular and sublobular bile ducts. The intrahepatic bile ducts communicate with the right and left extrahepatic ducts. The extrahepatic ducts usually unite to form one hepatic duct which joins the cystic duct of the gallbladder to form the common bile duct. Occasionally the hepatic ducts join the cystic independently, at different points, to form the common bile duct. The common bile duct, either after joining with the pancreatic duct or independently, opens into the duodenum at the ampulla of Vater, about 3½ inches (approximately 9 cm.) from the pylorus, where the ampulla is surrounded by the sphincter of Oddi, in the musculature of the duodenal wall. The bile ducts are lined with columnar epithelium and contain branched tubular glands, the ducts of which open on the surface of the columnar epithelium into the lumen of the common bile duct. The secretion of these glands dilutes the bile in the bile ducts after it has left the gallbladder.

Constituents of Bile. The total amount of bile eliminated by the liver of a normal adult human being in twenty-four hours varies between 500 and 1,000 cc. Bile is an excretory vehicle for various substances introduced into the body; for example, dyes, pigments and certain toxins that may be introduced into, or may have their origin in, the body under various circumstances.

The constituents of bile are: (1) bile pigments (bilirubin and its derivatives), (2) bile salts (taurocholates and glycocholates) and bile acids, (3) lecithin and cholesterol, (4) inorganic salts, (5) water (content about 97.5 per cent).

Of the foregoing, bile pigments, bile salts and cholesterol will be briefly discussed.

Bile Pigments. Manufacture of bile pigments is carried on in the cells of the reticuloendothelial system wherever they are present—in the bone marrow, spleen, liver, lymph nodes, certain connective tissue cells and so on. Bile pigments are produced from hemoglobin and myoglobin. By hydrolysis the hemoglobin is broken down to hematin and by further hydrolysis to bilirubin. Bilirubin, a globin-free, iron-free fraction of hemoglobin, is excreted by the liver through the biliary apparatus into the gastrointestinal tract where it is reduced to urobilinogen (stercobilin). On standing and exposure, urobilinogen is oxidized to urobilin. If, through infection or otherwise, bilirubin is exposed to oxidative agents while in the biliary apparatus, it becomes converted to biliverdin and, on further oxidation, to bilicyanin.

In the metabolism of bile pigments it is believed that the parenchymal cells of the liver absorb the hemobilirubin manufactured from hemoglobin by the reticuloendothelial system. These hepatic parenchymal cells change the hemobilirubin into cholebilirubin by removing the protein component. The cells then excrete the cholebilirubin into the bile capillaries which carry it to the duodenum, where it undergoes the changes already described.

Space does not allow discussion of the excellent elaborate study recently made by Watson and his associates on the derivatives of bile pigments. For helpful details the reader is referred to the work of these authors.[56–60]

Minkowski and Naunyn[61] produced intravascular hemolysis by administration of arseniuretted hydrogen. They caused intense jaundice in intact but not in hepatectomized ducks and geese. They concluded, therefore, that the liver was the sole center for the manufacture of bile. This was a vital issue for several years until M'Nee[62] and others confirmed the work of Minkowski and Naunyn but gave a different explanation for the findings. M'Nee stated that hepatectomy in fowls removed the reticuloendothelial cells of Kupffer and, consequently, bile pigments could not be formed and jaundice did not develop. It so happens that in ducks and geese the liver is the chief center of the reticuloendothelial system while in other animals the Kupffer cells of the liver form only a small part of the reticuloendothelial system. Mann, Bollman and Magath,[63] in 1924, gave ultimate proof that the reticuloendothelial system, not the liver, is the manufacturing center for bile pigment. They hepatectomized dogs and still obtained large amounts of bile pigment in the blood. In 1926 Mann, Sheard and Bollman[64] demonstrated spectrophotometrically that most of the bile pigments are formed by the reticuloendothelial cells of the bone marrow and spleen, the liver being a minor source. The

various aspects of recent research in this field warrant the following conclusions concerning the origin of bile pigments and the role played by the liver in that regard:

Bile pigments are manufactured by the cells of the reticuloendothelial system wherever they may be (in the bone marrow, liver, spleen, lymph nodes, certain connective tissue cells, and so on). The Kupffer cells of the liver, which are a part of the reticuloendothelial system, are those concerned with the manufacture of bile pigments. Hepatic parenchymal cells do not manufacture bile pigments; they excrete them. Therefore, bile pigments are formed both within and without the liver, and are normally excreted by the liver into the intestinal lumen through the biliary apparatus.

Bile Salts and Bile Acids. The cells of the liver are, as far as present knowledge indicates, wholly responsible for the production of bile salts and bile acids. It is believed, further, that bile salts have a significant influence on the function of hepatic parenchyma. The Kupffer cells of the liver also form and destroy bile salts. Müller[65] demonstrated that, after extirpation of the livers of frogs, there was no more accumulation of bile salts in the blood. The work of Bollman and Mann[66] indicates that the liver is not only the site of excretion but also the site of formation and destruction of bile salts. After removal of the liver injected bile salts are quantitatively eliminated through the kidney. The formation of bile salts decreases in an animal in which an Eck fistula has been made and in most conditions that produce hepatic injury[67] (exposure to chloroform, carbon tetrachloride and so forth). Diet plays an important part in the daily amount of bile salts eliminated by the liver into the intestine. Meat and butter in the diet increase the output of bile salts; hunger and starvation decrease it. Most of the bile salts excreted into the intestine are reabsorbed and exert their effect again on the liver. When they are eliminated by the liver again they once more perform their functions in the intestine.

Cholesterol. The term, "cholesterol," is derived from Greek elements which mean "solid bile." Cholesterol is the main constituent of gallstones. It is an important constituent of the lipids of all organs generally, and of the brain especially. In fact, it appears to be an essential constituent of all body fluids and cells. The cholesterol of the body is derived from both exogenous and endogenous sources. It is being continually synthesized, and also destroyed, within the body under normal conditions. It is present in both the free state and in combination with fatty acids as esters. In normal human blood serum the cholesterol present amounts to 150 to 300 mg. per 100 cc. but this is subject to considerable physiologic fluctuation. More than half of it (60 to 80 per cent) is in the form of esters. In bile and in the red blood cells it is present as free cholesterol only. The concentration of cholesterol esters in tissues is subject to considerable variation. It can be generally stated that all the cholesterol in bile, and practically all in red blood cells, and some 40 per cent of that which is in blood plasma, is in a free state.

For the absorption of ingested cholesterol the presence of bile and pancreatic juice is essential. Combination of cholesterol with bile acids makes them water-soluble and consequently absorbable. Pancreatic and intestinal enzymes (esterases) hydrolyze the cholesterol esters, which are resynthesized before reaching the lymph stream. Some cholesterol is absorbed directly into the blood stream but the chief route of its absorption is through the lymph channels. The blood contains enzymes which can split and resynthesize cholesterol esters. The idea that cholesterol is eliminated chiefly in the bile has been disproved. Some of it is completely destroyed in the body; a little is eliminated in the urine in conjugation with other compounds; a good share is eliminated in the bile; a little is lost in the desquamation of the skin; some is secreted with the milk but the largest amount is eliminated through the intestine as beta-cholestanol and as coprosterol. The latter is produced by the action of anaerobic bacteria. Cholestanol is a dihydro derivative, a reduction product, of cholesterol and a stereoisomer of coprosterol.

Knowledge regarding the function of cholesterol in the body is meager. Evidence is appearing to indicate that vitamin D and its provitamin are derived from cholesterol. It may act as an insulating medium for the myelin sheaths of nerves. Some believe that cholesterol plays a role in the regulation of cell permeability and membrane equilibrium. It has an antihemolytic action against venom, toxins, bile salts, saponins, soaps and so on. Cholesterol counteracts lysolecithin or lysocephalin, which is the hemolytic substance in certain venoms. There is an old belief that cholesterol has something to do with immunologic reactions in the

body. This is the basis for another old belief that a normal amount of cholesterol in the body is helpful against infection.

The metabolism of cholesterol is a controversial subject still under investigation and too complex to be reviewed here.

Functions of Bile Salts. Even though bile pigments are of great importance clinically for recognition of the presence and of the types of jaundice, physiologically they are merely waste products, to which the brownish color of human excreta is attributed. The bile salts in bile are the substances that are of physiologic importance. Following are the important extrahepatic functions of bile salts:

1. In the gastrointestinal tract bile salts aid in the emulsification, digestion and absorption of fats. Bile acids and salts lower surface tension and consequently leave the material with which they are mixed in a state of fine emulsion. This renders particles of fat more vulnerable to the action of lipolytic enzymes. Furthermore, even though bile does not in itself contain digestive enzymes, bile salts are activators of enzymes, especially of pancreatic lipase. Through the hydrotropic action of bile salts, fatty acids are made water-soluble and, consequently, absorbable.

2. It is evident that bile salts aid in the various phases of emulsification, digestion and absorpion of fats and, through their hydrotropic action, make most fat-soluble substances, such as cholesterol and fat-soluble vitamins, water-soluble and absorbable. This is the basis for the statement that the presence of bile salts is necessary for absorption of cholesterol and of fat-soluble vitamins (A, D, E and K). That bile indirectly acts as an antirachitic substance is evident because, in its absence, there is interference with absorption of vitamin D and fatty acids. The result is that calcium and magnesium in the intestine react with the fatty constituents in the gut, form soaps, and the calcium is therefore insufficiently available for formation of bone. This explains, at least in part, the demineralization of bone and the bony deformities which appear when bile has long been absent from the gastrointestinal tract.

3. Bile salts indirectly regulate the bacterial flora of the gut. By facilitating digestion and absorption of fats the digestion and absorption of other food materials is also facilitated and putrefactive processes are reduced to a minimum. Thus intestinal activity is least disturbed in the presence of normal amounts of bile.

4. The occurrence of hemorrhagic diatheses in the presence of severe hepatic damage, or of obstruction to the biliary passages, is basically explained as follows: First, in order for the liver to be able to manufacture prothrombin vitamin K must be available in the system. When damage to hepatic parenchyma is severe, however, even though vitamin K may be available, the liver cannot manufacture enough prothrombin for normal coagulation of the blood. When the biliary passages are completely obstructed bile salts are absent from the intestinal tract and fat-soluble vitamin K (natural compound) cannot be absorbed, at least in sufficient quantities. In either case (hepatic injury or biliary obstruction) hypoprothrombinemia results and a hemorrhagic tendency supervenes.

5. Bile salts act on the liver as highly effective choleretics and render the liver more efficient in excreting bile.

Factors Which Influence Production, Secretion and Elimination of Bile. Circulatory, nervous, chemical, dietetic and emotional factors have an important influence on the secretion and elimination of bile.

Circulatory Factors. An increase in blood flow to the liver increases the formation of bile. Intravenous administration of bile acids (dehydrocholic acid) increases the flow of hepatic arterial blood and consequently increases the production of bile by the liver.[34,68] Some say that as long as the arterial blood supply to the liver is intact, secretion of bile continues. However, occlusion of the hepatic artery does not prevent formation of bile.[18] Also, occlusion of the hepatic artery after excision of the hepatic nerves increases the flow of bile.[69] Increasing the portal blood flow augments the output of bile. Sudden, complete occlusion of the portal vein causes the output of bile to be reduced 50 per cent.

Nervous Factors. Section of the splanchnic or hepatic nerves leads to an appreciable increase in flow of bile which lasts for several hours. Stimulation of these nerves decreases flow of bile. This reduction may be through the influence of these nerves on the blood supply to the liver. Earlier work[70–71] indicated that section of the hepatic nerves caused no significant change in flow of bile. Stimulation of hepatic branches of the vagus nerve increases flow of bile.

Chemical Factors, Including Drugs. Choleretics are substances which augment the flow of bile by

stimulating the liver to produce more bile. They act by providing the liver with substances essential to the formation of bile. In other words, such substances are cholopoietic. *Cholagogues* are agents which stimulate the emptying of the gallbladder. They are cholekinetic; that is, they lead to mechanical expulsion of bile already present in the gallbladder and biliary passages.

Certain substances, for example magnesium sulfate, act as cholagogues by stimulating gastric, pancreatic and duodenal secretions and thus liberate agents which act as cholagogues. Magnesium sulfate also relaxes the sphincter of Oddi. Egg yolk and olive oil act both as cholagogues and as choleretics. Secretin, a hormone liberated from the intestinal mucosa, in addition to its stimulation of pancreatic secretion and intestinal secretion (succus entericus), is also a physiologic stimulant to the secretion of bile. Salicylic acid acts as a choleretic.[72] Acetyl salicylic acid (aspirin) increases the volume of bile formed under its influence by about 60 per cent. The water content of bile is especially increased and that is the reason for the statement that aspirin is definitely choleretic.[73] Some, however, have found no constant effect of salicylates on output of bile.[74] Cinchophen and its derivatives are hydrocholeretic; that is, they increase the volume flow of bile but decrease the solid content.[75] Pilocarpine, acetylcholine, insulin and choline also increase the flow of bile.[76] Histamine increases the production of bile, especially of bile salts.[77–81]

The effects of morphine on secretion of bile are somewhat contradictory. Rutherford (1878) did not think it had any appreciable effect. Others have reported decrease in secretion of bile after injection of small doses of morphine.[75,82,83] Morphine, 20 mg., given subcutaneously, has completely stopped the flow of bile. This was attributed to spasm of the sphincter of Oddi.

Dietetic Factors. A reciprocal interrelationship appears to obtain between the glycogenic and bile secretory functions of the liver. The digestion of carbohydrates has neither cholagogic nor choleretic effects. The majority of reports indicate that carbohydrates exert a depressing effect on the bile secretory activity of the liver.[84–87] The greater the quantity of glucose administered, the more evident is the depressant effect on secretion of bile.

Proteins have a definitely stimulating effect on the secretion of bile by the liver.[72,74,84,87,88] A high protein diet, especially of meat and liver, produce a maintained increase in flow of bile.

Fats are very strongly cholagogic and also somewhat choleretic. A fatty meal also relaxes the sphincter of Oddi. The slightly choleretic effect of fatty meals is attributed to the proteins present.[85] Boyden, however, has expressed the belief that a fatty meal is choleretic.[89]

Emotional Factors. Rage suppresses the flow of bile in a dog with a fistula.[90] Pain has similar effects. "Emotional catarrh," and the associated jaundice, is believed to be due to the inhibitory effects of anger on flow of bile. Vomiting is a very strong stimulant to flow of bile.[91]

Mechanism of Secretion of Bile. Bile is continuously secreted by the liver, even during fasting.[87] The basal secretion varies with blood flow and other factors, such as those already specified, and is affected by stimulation of the secretory fibers of the vagus nerve. The liver can continue secreting bile even though the pressure in the duct system may reach 250 or 300 mm. of water. With higher pressures secretion of bile ceases and jaundice appears shortly thereafter. Under normal conditions the sphincter of Oddi, surrounding the entrance of the common bile duct into the duodenum, is tonically closed. The bile removed from the blood by the parenchymal cells of the liver is squeezed out of the intracellular bile vacuoles through the bile canaliculi into the bile capillaries that lie between the hepatic parenchymal cell cords. From there it is extruded into the sublobular and other ducts within the substance of the liver until it reaches the right and left hepatic bile ducts. The continually secreted bile fills the duct system until the pressure reaches 50 to 70 mm. Then the bile passes through the cystic duct into the gallbladder, where it is stored. The amount of bile secreted by the liver during an average twenty-four hours is about 500 to 1,000 cc.

Anatomy of Gallbladder Relevant to Secretion of Bile. The capacity of the human gallbladder is about 50 cc. Its wall is made up of a thin layer of smooth muscle fibers and fibro-elastic tissue. It is lined by mucosa surmounted by a layer of columnar epithelium. The cystic duct, the mucosal lining of which is made up of tortuous spiral folds (valves of Heister), joins the hepatic duct at an acute angle to form the common bile duct, which in turn passes obliquely through the muscular wall of the duodenum to the ampulla of Vater.

Functions of Gallbladder. Certain animals (whale, elephant, deer, horse and rat) do not possess a gallbladder. Some human beings, also, who for one reason or another have been deprived of their gallbladders, are able to enjoy a reasonably normal life thereafter. Nevertheless, it should not be overlooked that the gallbladder has certain important functions and should be removed only for adequate reasons. These functions include: (1) It acts as a reservoir for bile which is continually secreted by the liver. (2) It is a regulator of bile pressure in the bile duct system. After cholecystectomy the reservoir and regulator of pressure in the biliary system is removed and consequently the remaining bile ducts dilate. (3) The gallbladder concentrates bile about ten times. The gallbladder can hold about 50 cc. of concentrated bile; thus it can accommodate practically all bile secreted by the liver in twenty-four hours. Water and inorganic salts are reabsorbed from the bile by the mucosa of the gallbladder, and through its lymphatics and blood vessels this water and inorganic salts are returned to the circulation. This explains the syrupy, thick, dark characteristics of the bile obtained from the gallbladder. Inflammation of the gallbladder abolishes or reduces its ability to concentrate bile. (4) The gallbladder secretes mucin into the bile that is stored in its lumen. The importance of this is not clear; some believe mucin acts as a lubricant, others say it inhibits further production when bile is in excess. (5) One of the major functions of the gallbladder is the ejection of bile into the gastrointestinal tract at the peak of digestion where and when it is most greatly needed.

Mechanism of Emptying of Gallbladder. During fasting the gallbladder becomes gradually distended with the bile which is continually coming to it from the liver. The gallbladder acts on this bile in the ways described. It has been established that contractions of the wall of the gallbladder are chiefly responsible for evacuation of bile from the gallbladder. The time of emptying is definitely related to meals. Fatty foods have been found to be the most effective stimulus. Protein and carbohydrates are reported to have no effect on evacuation of the gallbladder. Products of fat digestion, and magnesium sulfate or hydrochloric acid, when introduced into the duodenum bring about contraction of the gallbladder, relaxation of the sphincter of Oddi and consequently evacuation of bile from the gallbladder into the intestine.

There are two mechanisms which participate in controlling evacuation of the gallbladder; namely, a nervous and an hormonal mechanism.

1. Experimental evidence suggests that intrinsic and extrinsic nervous influences participate in the mechanism of emptying of the gallbladder; Westphal[92] demonstrated the intimate nervous connections of the gallbladder with the parasympathetic nerves (vagus) and with the sympathetic nerves (splanchnics). Stimulation of the vagus produces contraction of the gallbladder and increases flow of bile through the sphincter of Oddi. If the stimulus is very strong, the sphincter may contract and increase the pressure within the gallbladder and duct system. Stimulation of the sympathetic nerve supply leads to relaxation of the wall of the gallbladder. Moderate contraction of the gallbladder, from stimulation of either sympathetic or parasympathetic nerves, has been reported.

2. Hormonal influences on emptying of the gallbladder are more important than the nervous influences. This becomes evident after the nervous connections have been severed and fatty food is introduced into the duodenum. Boyden[93–95] reported that blood taken at the height of digestion from one animal caused rapid evacuation of the gallbladder of a fasted animal which received the blood in transfusion. Blood from a fasted animal had no effect. Ivy and Oldberg[96–97] obtained an acid extract from the mucosa of the upper part of the intestine and produced contraction of the gallbladder by administering the extract intravenously. Intravenous administration of acid, or of fat and fatty compounds, did not cause contraction of the gallbladder. This led to the assumption (which proved to be correct) that on introduction of substances such as acid chyme or fatty foods into the duodenum, a hormone is liberated by the intestinal mucosa. The hormone is absorbed into the circulation and is carried in the blood stream to the gallbladder, causing its contraction and consequent evacuation. This hormone is related to, but is not, secretin. Ivy and Oldberg gave it the name "cholecystokinin." The effects of the purified substance have been demonstrated on man. Blood taken from man at the peak of digestion of yolk of egg, if given to another man as a transfusion, produced evacuation of the gallbladder of the recipient. Blood from a fasted donor had no such effect. This result is similar to that obtained by Boyden in animals.

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Clinico-pathologic Conference

Hepatic Insufficiency

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, J. M. (No. 226207), was a white single high school girl, seventeen years of age, who was first admitted to the Barnes Hospital on August 16, 1953, because of excessive weakness, anorexia, abdominal distention and discomfort.

The patient had been well until early in March, 1953, when she noted unusual and extensive fatigue. After returning home from school in the afternoon she would sleep two to three hours before her evening meal, whereas she had formerly been accustomed to playing actively during the period after school. Nonetheless, neither she nor her parents became concerned about this change until a month before admission when the patient began to complain of fullness and heaviness in the abdomen. Her appetite continued to be good, however, and she had no nausea, vomiting, diarrhea, constipation or weight loss. In April, 1953, she was seen by a physician who told her that she suffered from gaseous distention. He prescribed antacid preparations which afforded no relief; indeed, the abdominal discomfort became more troublesome and anorexia developed. In May, 1953, another physician was consulted. He noted that the patient had massive ascites and referred her to the Jewish Hospital of St. Louis for diagnostic studies. There she was found to have, in addition to ascites, hepatosplenomegaly and distention of venous collaterals in the abdominal wall, but no icterus, spider angiomas or peripheral edema.

Laboratory data at the Jewish Hospital provided the following information: hemoglobin, 12.0 gm. per cent; white blood cell count, 7,250; differential count: eosinophils, 2 per cent; stab forms, 2 per cent; segmented neutrophils, 58 per cent; lymphocytes, 34 per cent; monocytes, 4 per cent; icterus index, 10 units; total serum protein, 6.3 gm. per cent; albumin, 3.4 gm. per cent; globulin, 2.9 gm. per cent; prothrombin time, 30 per cent of normal; serum cholesterol, 98 mg. per cent; cephalin-cholesterol flocculation test, 4 plus; bromsulfalein retention, 48 per cent at thirty minutes; alkaline phosphatase, 13.9 Bodansky units; first and second strength tuberculin tests, negative; roentgenograms of the chest and of the upper gastrointestinal tract: no abnormalities. Bone marrow examination: cellular marrow with normal representation of all cells.

The patient remained in the Jewish Hospital for three weeks during which time she had several paracenteses. Each time between 2 and 3 L. of clear amber fluid with a specific gravity of 1.012 were removed. She was given a high protein, high carbohydrate diet with vitamin supplements and her salt intake was restricted. In addition she received vitamin K and crude liver extract parenterally every other day and mercurial diuretics frequently.

Following discharge from the hospital the patient ate poorly. The ascitic fluid reaccumulated at a rapid rate so that paracenteses were required at seven to ten-day intervals. Fetor hepatis was noted. Early in July, 1953, cationic exchange resins were administered in an effort to control the ascites and the interval between paracenteses lengthened to four weeks.

On August 5, 1953, a paracentesis was performed and 5 L. of clear yellow fluid with a protein content of 1.5 gm. per cent and sodium of 121.8 mEq./L. were removed. Examination of the sediment of this fluid revealed no cells. Concomitantly the serum sodium was found to be 130.6 mEq./L. and the chloride 103 mEq./L. Fluid drained from the paracentesis wound for the following week, and during this period the patient found it increasingly difficult to take food. She had several episodes of diarrhea, passing four to six watery stools per day, and she became extremely weak. Because of the progression of her symptoms she was referred to the Barnes Hospital on August 16, 1953, for further study.

Careful review of the past history revealed that prior to the present illness the patient had never had jaundice, hematemesis, melena or anorexia. In infancy a "blood vessel tumor" had been removed from her face. During the first year of life she had frequent bouts of diarrhea which were said at that time to have been due to food intolerance, but she subsequently had not had diarrhea until the present illness, and her appetite and food intake had been entirely normal as had been her growth and development. In July, 1949, while she was in Florida, the patient developed anorexia, nausea, a sore throat and cough and was hospitalized. A transcript of her hospital record was obtained and indicated that the chief physical findings at that time were injection of the pharynx, hypertrophy of the tonsils and the presence of a few coarse rales in the lungs. The significant laboratory data included an increase in the number of lymphocytes in the differential smear and a positive heterophil agglutination test in a titer of 1:320. A diagnosis of infectious mononucleosis was made and the patient was treated with antibiotics and bed rest. She apparently recovered without residual. In December, 1952, she had "sinusitis" and was given two injections of penicillin by a physician. No other history of recent injections or of exposure to hepatotoxic agents could be elicited.

Physical examination at the time of her admission to the Barnes Hospital revealed her temperature to be 37°c., pulse 80, respirations 15 and blood pressure 100/70. The patient was an alert, friendly and cooperative girl. There was evidence of wasting of the muscle mass of both the arms and upper chest. The veins over the chest and abdomen were dilated. The abdomen was protuberant and the flanks bulged. A fluid wave was easily demonstrated. A mass, thought to be the spleen, was felt in the left upper quadrant and the liver edge was palpable 3 cm. below the right costal margin. There was minimal ankle edema. Otherwise the physical examination was within normal limits.

The laboratory data were as follows: red blood cell count, 6,100,000; hemoglobin, 15.6 gm. per cent; white blood cell count, 15,400; differential count: 4 per cent metamyelocytes, 9 per cent stab forms, 54 per cent segmented neutrophils, 29 per cent lymphocytes and 4 per cent monocytes. Urinalysis: specific gravity, 1.011; protein, negative; sugar, negative; centrifuged sediment, 4 to 6 red blood cells and 8 to 10 white blood cells per high-power field. Stool: negative. Cardiolipin test: negative. Blood chemistry: non-protein nitrogen, 20 mg. per cent; fasting blood sugar, 75 mg per cent; sodium, 128.6 mEq./L.; potassium, 5.5 mEq./L.; chloride, 92 mEq./L.; carbon dioxide combining power, 29.4 mEq./L.; total protein, 5.4 gm. per cent; albumin, 3.1 gm. per cent; globulin, 2.3 gm. per cent; alkaline phosphatase, 4.6 Bodansky units; cholesterol, 123 mg. per cent; cephalin-cholesterol flocculation test, 3 plus; thymol turbidity test, 3.7 units; total bilirubin, 2.45 mg. per cent; sodium bilirubinate, 0.9 mg. per cent; bilirubinglobin, 1.55 mg. per cent; prothrombin time, 26 per cent of normal. Electrocardiogram: within normal limits. Roentgenogram of the chest: negative except for elevation of the diaphragms.

The patient was given a high protein, high vitamin diet and received injections of vitamin K and crude liver extract. She was discharged from the hospital on August 21, 1953, to follow the regimen outlined, and to be seen frequently as an outpatient.

After discharge the patient did well until about seven days before her second and last admission when she began to complain of upper abdominal pain. Marked relief from her discomfort followed paracentesis but during the next several days she felt extremely weak and was constantly nauseated. The serum sodium was determined and found to be 131 mEq./L. Because it was thought that her symptoms might be due to an electrolyte imbalance she was given 5 gm. of sodium chloride daily by mouth in the form of enteric-coated tablets. Soon after beginning this medication she developed persistent diarrhea and became progressively weaker and more lethargic. On the day before entry her appetite decreased markedly and she developed severe, constant abdominal pain. Fluid, which had been draining from the paracentesis site for about six days, became foul smelling, and on August 31, 1953, she was readmitted.

Physical examination at this time revealed her temperature to be 37.2°c., pulse 100, respirations 20 and blood pressure 80/60. The patient was lethargic, appeared acutely ill and complained of abdominal pain. Two small spider angiomas were seen, one on the face and the other on the left shoulder. The abdomen was protuberant and there was generalized abdominal tenderness and rebound tenderness on palpation. The bowel sounds were audible.

Thin, clear, foul smelling fluid was discharging from the site of the last paracentesis. The physical examination was otherwise negative.

The laboratory data were as follows: red blood cell count, 7,370,000; hemoglobin, 17.5 gm. per cent; white blood cell count, 22,000; differential count: 2 per cent stab forms, 54 per cent segmented neutrophils, 43 per cent lymphocytes and 1 per cent monocytes. Urinalysis: specific gravity, 1.026; protein, negative; sugar, negative; centrifuged sediment, 10 to 20 red blood cells and 5 to 10 white blood cells per high-power field. Stool: negative. Blood chemistry: sodium, 113 mEq./L.; chloride, 93 mEq./L.; non-protein nitrogen, 34 mg. per cent; total protein, 3.7 gm. per cent; albumin, 1.7 gm. per cent; globulin, 2.0 gm. per cent; cholesterol, 73 mg. per cent; alkaline phosphatase, 4.1 Bodansky units; total bilirubin, 3.38 mg. per cent; sodium bilirubinate, 0.62 mg. per cent; bilirubinglobin, 2.76 mg. per cent. Electrocardiogram: sinus tachycardia.

Immediately upon admission the patient was given fluids and vitamins parenterally, and a high protein diet was prescribed. Cultures of the fluid discharging through the paracentesis wound revealed a non-hemolytic coagulase-negative staphylococcus citreus. Therapy was directed toward restoration of a normal electrolyte pattern but in spite of the administration of large amounts of fluids and electrolytes this aim was not achieved. (Table 1.) Two days after admission the patient's blood pressure suddenly became unobtainable and her pulse rate rose to 145 per minute. She was obtunded but could be aroused and was able to talk rationally. Nor-epinephrine was given intravenously, the blood pressure returned to normal levels, and the patient became more alert and comfortable. Subsequently, however, constant infusion of nor-epinephrine was necessary in order that the blood pressure be maintained at normal levels. Because it was believed that the underlying cause of the patient's disease conceivably could be some chronic granulomatous infection she was given 1 gm. of streptomycin and 2 gm. of choramphenicol daily. Her condition continued to grow progressively worse, however, and was not favorably influenced by the administration of 25 mg. of corticotropin intravenously. The eosinophil count was 55 per cu. mm. before and 0 after administration of the latter drug.

Two days before the patient's death she received 150 cc. of salt-free serum albumin intravenously and on the day before death whole blood transfusions were instituted. On that day, for the first time, a loud high pitched systolic murmur was heard over the apical area and the left border of cardiac dullness was noted to be in the anterior axillary line. There were no other significant changes in her status, however. On the day of death, September 6, 1953, the

TABLE 1

Day	1	2	3	4	5	6	7
Fluid intake (cc.):							
Oral	1,500	1,700	2,240	1,100	240	2,00	.....
5% glucose in 0.9% NaCl	1,000	1,000	2,000	1,000	.....	2,000	.....
5% glucose in HOH	.....	.....	.....	2,000	2,000	.....	.....
Molar sodium chloride	.....	230	.....	500	100	.....	.....
Molar sodium lactate	225	.....	.....	.....	.....	.....	.....
Serum albumin or whole blood	.....	.....	250	.....	150	500	500
Total	2,725	2,930	4,490	4,600	2,490	2,700	1,000
Output (cc.):							
Urine	?	235	600	450	400	400	.....
Emesis or Levine tube	100	.....	.....	.....	.....	200	.....
Ascitic fluid?	.....	.....	.....	.....	.....	.....	.....
Blood sodium in mEq./L	113	120	124	118.3	123.6	.....	.....
Blood potassium in mEq./L	.....	7.6	5.9	7.4	5.3	.....	.....
Blood chlorides in mEq./L	93	.....	.....	81	.....	.....	.....
Blood CO_2 in mEq./L	.....	.....	.....	25.2	.....	.....	.....
Rbc in millions/cu. mm.	.....	7.37	.....	5.86	5.73	.....	.....
Hg in gm./100 cc.	.....	17.5	.....	17	12.8	.....	.....

patient was found to require increasing amounts of nor-epinephrine. She began to complain of severe dyspnea and developed marked tachypnea but the lungs continued to be clear to auscultation. While she was receiving the second unit of whole blood she suddenly became extremely dyspneic and anxious and rales were heard over both lungs. She developed a cough productive of frothy, bloody sputum. Despite emergency measures including positive pressure oxygen, digitalis and aminophyllin intravenously, and the use of rotating tourniquets on the extremities the patient became rapidly worse, experienced a generalized convulsion and expired.

CLINICAL DISCUSSION

DR. CARL V. MOORE: The protocol presents an accurate picture of this unfortunate girl's illness. I should like to add only one point which is perhaps not at once obvious. During the last six to eight weeks of the patient's life it became extremely difficult to obtain blood by venepuncture. When blood was drawn for various laboratory procedures, it had to be obtained from the femoral veins, and when fluid was given intravenously it was necessary that a surgical "cut-down" be performed. Consequently, and understandably, the house staff attempted to keep a given channel available by administering small amounts of fluid continuously. It was clear that the patient's course represented one of progressive hepatic failure but she received thoughtful, attentive care from her physician, and there were long periods of time when at least one member of the staff stayed at her bedside. Before we begin the general discussion, Dr. Wilson, would you care to discuss the roentgenographic findings?

DR. HUGH M. WILSON: As indicated in the protocol the roentgenographic findings were of little help. The examination of the chest was negative except for elevation of the diaphragms due to the presence of fluid in the abdomen. Films of the upper gastrointestinal tract were negative and flat films of the abdomen revealed floating loops of small enlarged bowel, a typical finding in the presence of ascites.

DR. MOORE: I believe that our discussion should be divided into three major parts: first, the differential diagnosis; second, the course of the disease; and third, the nature of the terminal episode. In Table II I have listed the diagnoses which were thought of by the physicians who cared for this patient. Viral hepatitis, presumably the epidemic type, was an important possibility; but because the patient had received several injections of penicillin about four months before she became ill, homologous serum hepatitis with subacute necrosis also was included. Four years earlier she had had what was apparently infectious mononucleosis and the possible relationship of the subsequent hepatic disease to infectious mononucleosis was considered. Other possibilities mentioned were primary carcinoma of the liver, some granulomatous disease of the liver and finally Chiari's syndrome. Dr. Karl, I know that you saw this patient. Would you please begin the discussion?

TABLE II

DIAGNOSES CONSIDERED BY PHYSICIANS

Viral Epidemic Hepatitis
Homologous Serum Hepatitis
Infectious Mononucleosis with Hepatitis
Carcinoma of the Liver
Granulomatous Liver Disease
Chiari's Syndrome

DR. MICHAEL M. KARL: When I first saw the patient in May, 1953, there was both clinical and laboratory evidence of diffuse hepatocellular damage—ascites, some increase in the collateral circulation over the abdomen, a palpable spleen, a 4 plus cephalin-cholesterol flocculation test and marked retention of bromsulfalein.

DR. MOORE: Of the various possibilities shown in Table II, Dr. Karl, which seemed most likely to you?

DR. KARL: I thought she probably had chronic hepatitis or post-necrotic nodular cirrhosis. There was no distinct episode suggestive of epidemic viral hepatitis except the illness four years previously when the diagnosis of infectious mononucleosis was made. Because she apparently had recovered completely and uneventfully from that episode and because there was no other illness compatible with viral hepatitis, Chiari's syndrome with thrombosis of the hepatic veins and subsequent hepatocellular damage also came to mind. Statistically, post-necrotic nodular cirrhosis secondary to viral epidemic hepatitis is much more common.

DR. MOORE: It is conceivable, is it not, that the patient had unrecognized viral hepatitis or else that the period early in 1953 when she was excessively fatigued may have represented the insidious onset of the disease.

DR. KARL: Yes, either possibility is reasonable.

DR. MOORE. Dr. Shank, would you continue the discussion?

DR. ROBERT E. SHANK: It was our impression that this patient had subacute hepatic necrosis, presumably secondary to viral hepatitis. We postulated, as you just suggested, that the time when she first began to complain of fatigue and abdominal pain marked the insidious onset of hepatitis. As has been stated, the fact that the patient received several penicillin injections four months before she became ill brought up the possibility of homologous serum hepatitis, but we believed it more likely that she had viral hepatitis of the epidemic type.

DR. MOORE: Did you seriously consider either primary carcinoma of the liver or a granulomatous disease?

DR. SHANK: We thought both merited mention but we were unable to muster evidence substantiating either one. With either process one would have expected an illness characterized by fever, and yet this patient was afebrile until the last few days of her life. Further, she had no lesions in the lungs or lymph nodes and tuberculin skin tests performed while she was in the Jewish Hospital were negative. With a granulomatous disease more pronounced hepatic enlargement would be expected. Primary carcinoma of the liver must always be considered when a patient presents evidence of hepatic damage and a rapidly downhill course. On the other hand, there was no history of previously existing liver disease; and although hepatomas do occur in early life, in such cases it is presumed that they have arisen from embryonic rests rather than because of underlying cirrhosis. Finally, in my experience the alkaline phosphatase is often high in carcinoma of the liver. It was elevated when this girl was in the Jewish Hospital but was subsequently always normal. I think the lack of persistent elevation of alkaline phosphatase is evidence against the diagnosis of primary carcinoma of the liver.

DR. MOORE: Dr. Goldman, some years ago the subject of one of our clinicopathologic conferences was a man who died five or six months after the onset of an illness which was thought clinically to have been subacute necrosis of the liver or a primary carcinoma. At autopsy it was found that this patient had extensive histoplasmosis of the liver without recognizable pulmonary involvement. Is histoplasmosis a likely possibility here?

DR. ALFRED GOLDMAN: I don't think so. As Dr. Shank has pointed out, the patient was afebrile during almost all of her illness; and although histoplasmosis may be limited to the liver and perhaps the spleen, patients usually present some evidence of infection, particularly fever. I don't recall having seen massive ascites of the degree present in this case in histoplasmosis.

DR. MOORE: Dr. Mendeloff, would you discuss the last diagnosis listed in Table II, namely, Chiari's syndrome?

DR. ALBERT I. MENDELOFF: That term has been used rather loosely to describe a number of syndromes characterized primarily by massive ascites and hepatosplenomegaly. Presumably the underlying lesion consists of thrombosis of the veins draining the liver. In some instances there is evidence of endophlebetic change, whereas in others apparently the thrombosis occurs without thrombophlebitis. When the diagnosis of Chiari's syndrome is suggested there is often evidence of an underlying disease in its late stages such as hepatic necrosis or cirrhosis. In this particular instance, it is conceivable that thrombosis of the hepatic veins occurred terminally, but I suggest that the thromboses were a secondary, late complication rather than the primary disease.

DR. MOORE: Dr. Sale, you also examined this patient and first detected the presence of an enlarged spleen.

DR. LLEWELLYN SALE, SR.: On the few occasions when I saw this young woman I was extremely confused as to the definitive nature of her disease. It was quite clear that she had hepatic insufficiency but I was never clear in regard to the underlying process. As has been mentioned, the possibility that infectious mononucleosis set off the untoward chain of events was considered but I have not encountered a convincing demonstration that the ultimate emergence of a terminal picture such as she showed may be secondary to infectious mononucleosis. It would seem very unusual that a period of four years would have elapsed between the bout of infectious mononucleosis and the terminal illness if the latter were a sequel to the former. On the other hand, I know no way to exclude that possibility. We have all seen hepatic involvement in infectious mononucleosis, and indeed jaundice occurs occasionally, but to my knowledge none of the patients I have seen has developed a subsequent clinical picture such as this girl exhibited.

DR. MOORE: Dr. Shank, would you say something about the relationship of infectious mononucleosis to serious liver disease?

DR. SHANK: Certainly observers in this country are in agreement that hepatic involvement does occur frequently in infectious mononucleosis. There is little evidence, however, that hepatic involvement in infectious mononucleosis constitutes the initiating lesion of subsequent cirrhosis, although there has been at least one case described in which cirrhosis of the portal type is presumed to have followed infectious mononucleosis. In the particular case to which I refer, however, the interpretation is open to question, in my opinion, because the patient had had an illness associated with jaundice several years before he developed infectious mononucleosis, and after the attack of infectious mononucleosis had been on a poor dietary regimen with an excessive intake of alcohol. Therefore, on the basis of that one case I would be unwilling to accept as fact the concept that infectious mononucleosis may lead to cirrhosis, but as Dr. Sale says, it is impossible to exclude that possibility. So far as our patient is concerned, I think it is important to note that, following her recovery from infectious mononucleosis in 1949, she was extremely active in sports and in other high school activities. It would be difficult to imagine that these activities would have been compatible with progressive liver disease over the period of four years during which she felt well. Consequently, I do not believe that her fatal illness was related to the earlier episode of infectious mononucleosis.

DR. MOORE. Recently in the literature considerable comment has been made concerning hepatitis of insidious onset. Its relation to age and sex has been noted. Because this form of hepatitis is almost always unrecognized, the patients are not kept at bed rest and the unfavorable course which most of them exhibit may be due, in part at least, to this factor.

DR. MENDELOFF: So-called hepatitis of insidious onset has been recognized for many years. The development of signs and symptoms of hepatic failure and of portal hypertension in patients in whom no previous acute attack of hepatitis can be identified is not an uncommon occurrence, and indeed has apparently been seen with increasing frequency. The recent literature leads me to believe that hepatitis of insidious onset is approximately three times as common in females as in males. Furthermore, it is my impression that severe hepatitis of all forms has a predilection for the female. The prognosis of hepatitis is especially poor when it develops in women past the menopause.

Dr. MOORE: In one report of an epidemic in Denmark all but 2 of 108 patients suffering from hepatitis of insidious onset were females. Do you have any explanations for the greater susceptibility of women to hepatitis?

DR. MENDELOFF: There is no answer to this question at present. Zondek suggested some years ago that an estrogen tolerance test might be valuable in defining hepatitis of insidious onset. As he acquired experience with the test, however, he was disappointed to find that the test was not useful, even in patients with viral hepatitis of the more common and more easily diagnosed variety. That the normal liver has a role in the metabolism of estrogens and other sex hormones is well known, but what happens to the metabolism of the various hormones in hepatitis is not well understood. With regard to the age incidence of the disease, most hepatitis of insidious onset, the more fulminating form of epidemic viral hepatitis, and subacute hepatitis are, according to recent reports and in our experience, too, more common in adolescent girls and in post-menopausal women.

DR. MOORE: Would patients with hepatitis of insidious onset have such unfavorable courses if the disease were recognized and the patients kept at bed rest? Certainly bed rest is an important measure in the treatment of patients with viral epidemic hepatitis?

DR. MENDELOFF: I don't believe there are adequate data to answer your question and one can only speculate. Bed rest, if instituted early, might well be of great benefit. The experience with the form of hepatitis characterized by an insidious onset is that jaundice is a late manifestation; by the time it occurs the liver has been severely compromised and the prognosis is extremely poor. One perhaps can draw an analogy between hepatitis of insidious onset and the so-called type 2 nephritis of Ellis.

DR. MOORE: Are there any other comments?

DR. HAROLD SCHEFF: Isn't it rare for jaundice to be absent in patients with post-hepatitic cirrhosis?

DR. SHANK: It is unusual but in a recent paper Baggenstoss reviewed forty-three cases of cirrhosis which apparently followed viral epidemic hepatitis. Two of the patients in his series had not been icteric. Further, as Dr. Mendeloff

has pointed out, subacute hepatic necrosis or post-necrotic cirrhosis does occur relatively frequently in patients with so-called hepatitis of insidious onset.

DR. FRANK NORBURY: Could the higher incidence of hepatitis in females be associated with the use of hair dyes, cosmetics or other hepatotoxins?

DR. MENDELOFF: Investigators interested in hepatic disease have been aware of the possible relation of certain cosmetics and dyes to liver damage but how well this specific point has been studied in the group of patients we are considering is not known to me.

DR. MOORE: In the present patient a careful history was taken in this regard and no evidence that she had been exposed to any hepatotoxin could be elicited.

DR. HENRY A. SCHROEDER: Is it possible that she could have had a hemangioma of the liver?

DR. MOORE: Dr. Schroeder's question presumably is related to the fact that a small tumor, possibly a hemangioma, was removed from the patient's face when she was a very young child.

DR. SHANK: We are aware, of course, that hemangiomas may occur in several sites in the same individual. This possibility was considered but the history of the illness was atypical for this type of tumor. Further, we were unable to hear a bruit or to feel pulsations in the liver and we dismissed that explanation as most unlikely.

DR. MELVIN L. GOLDMAN: A disease which can cause liver insufficiency without jaundice is amebic hepatitis. During World War II we saw a number of patients with clinical courses similar to this one. I doubt seriously that this girl had amebic hepatitis but I mention it for the sake of completeness.

DR. MOORE: Were amebae searched for in the patient's stool, Dr. Shank?

DR. SHANK: I don't believe that amebae were specifically looked for although a number of stool examinations were done. However, amebic hepatitis is usually associated with a much greater degree of toxicity than was present in this instance.

DR. MOORE: Let us now turn to the terminal episode. The patient was admitted to the hospital for the second and last time primarily so that an attempt could be made to re-establish normal electrolyte balance. Her serum sodium was low. It is presumed that when the serum sodium falls extracellular fluid moves into the cells, the plasma volume decreases and there is a rise in hematocrit. The circulation then slows, cardiac output decreases, the blood pressure falls and shock occurs. All of these changes occurred in the present case. The patient was lethargic, anorectic, nauseated and had some abdominal pain. On at least one occasion she complained of muscular cramps. These are clinical manifestations one sees in patients with the low salt syndrome.

Certain features of the terminal episode suggested adrenal insufficiency. Dr. Daughaday, before we discuss the low salt syndrome and the circulatory failure would you state your opinion as to whether or not this patient had adrenal insufficiency?

DR. WILLIAM H. DAUGHADAY: Some of the features of the terminal period, namely, the persistently low blood pressure and the difficulty in raising the serum sodium, despite adequate administration of sodium ions, are compatible with a diagnosis of adrenal insufficiency. Against that diagnosis, however, are the facts that many of the findings can be explained satisfactorily on another basis. The patient did not at any time have hypoglycemia nor did she exhibit increased pigmentation. Further, it would be most unlikely for a patient with Addison's disease to accumulate ascitic fluid at the rate this girl did. Finally, the hyponatremia of Addison's disease is almost always associated with a tremendous decrease in extracellular fluid volume. Consequently, it is rare to see a patient with uncompensated adrenal insufficiency who has edema.

DR. MOORE: Does the fact that the eosinophil count fell from 55 to 0 after the administration parenterally of 25 mg. of corticotropin help in ruling out the diagnosis of adrenal insufficiency?

DR. DAUGHADAY: That response constitutes important evidence that the patient still had functioning adrenocortical tissue. One point which I have mentioned at previous conferences is that a number of investigators hold that the adrenal cortex is involved in the fluid retention seen in cardiac failure and cirrhosis of the liver, mediation presumably being related to the adrenal cortical "salt hormone." There is good evidence that liberation of the salt hormone by the adrenal cortex is independent of the liberation of other recognized adrenocortical principles and probably not under the direct control of corticotropin. Thus it is entirely conceivable that although this patient did not have true

Addison's disease, that is, panhypoadrenocorticism, she may have had a disturbance in the salt hormone, customarily referred to as the "doca-like" hormone. Within the last few months it has been announced both in England and in Switzerland that a new adrenocortical steroid has been crystallized which is of great importance in salt balance. This newly defined hormone is said to have about thirty times the salt-retaining potency of desoxycorticosterone.

DR. MOORE: Dr. Furchgott of the Department of Pharmacology has been good enough to come to this conference and I would like to ask him if he would comment on the possible pathogenetic role of VDM in shock. During his association with Dr. Shorr at Cornell, Dr. Furchgott was an active participant in the studies done by Dr. Shorr's group on experimental shock.

DR. ROBERT M. FURCHGOTT: As you know, VDM stands for vasodepressor material, and is the designation which was assigned to this principle by Shorr and his co-workers at Cornell University Medical College. They isolated a substance from the serum of dogs in deep, irreversible shock which was presumably liberated from the liver. For a considerable period of time the presence of this substance depended on its identification by the so-called rat mesoappendix test, in which procedure serum from the dog in shock was injected into the rat. If VDM was present, the terminal arterioles in the meso-appendix exhibited decreased sensitivity to topically applied epinephrine. Subsequently VDM was identified as an iron containing protein of liver and spleen and called ferritin. Presumably in the presence of anoxia and shock some of this substance is released by the liver and blocks the normal vasoconstrictor mechanism in the peripheral circulation. It was our concept that the release of VDM was responsible for the irreversibility of shock, and we were able to show a temporal relationship between its occurrence and the onset of the irreversible stages of shock. Unfortunately, I don't believe satisfactory demonstration of the adverse effect of VDM on the peripheral circulation has been made except by the rat mesoappendix test.

DR. MOORE: That peritonitis had a significant role in the patient's death was not considered seriously by those taking care of her and I don't believe that possibility merits discussion at this point. On the other hand, therapy of the low salt syndrome was of obvious import and was directed toward the restoration of plasma volume and of serum sodium. It is of interest in this regard to ask why, if the plasma volume was low, transfusion of whole blood produced pulmonary edema. Dr. Daughaday, you saw this patient on her last admission. Would you comment on the treatment which was employed in the attempt to restore normal electrolyte balance.

DR. DAUGHADAY: As has been indicated, when this patient was admitted it seemed clear that she presented an example of the low salt syndrome. The sodium determination which was done after her admission was performed on a badly hemolyzed sample of blood obtained from the femoral vein. Perhaps the serum sodium was in fact not quite as low as was recorded. Sodium deficit was calculated on the basis of extracellular fluid and it was planned to check the serum sodium on the day following admission. Unfortunately, she received larger amounts of glucose than was originally planned because nor-epinephrine had to be given constantly and it was given in glucose. Nonetheless, she was also given large amounts of sodium and it is our belief that her failure to respond cannot be attributed to salt depletion only. Whole blood was administered at Dr. Carl Moyer's suggestion. He postulated that one of the factors contributing to her grave condition was poor renal function based on hypotension and a relatively ineffective plasma volume. It was thought that if the renal hemodynamics could be improved, the patient might herself contribute to readjustment of the electrolyte pattern. How low the patient's plasma volume was at the time the blood was started is a matter of question, I believe. I don't think that the hypotension was related solely to hypovolemia.

DR. MOORE: Dr. Schroeder, would you like to comment?

DR. HENRY A. SCHROEDER: I would take issue with Dr. Daughaday in that I don't believe the patient received adequate amounts of sodium. If one calculates the amount of sodium infused from the data given in Table I, he finds that she never received hypertonic saline, and it is impossible to raise plasma volume by giving hypotonic or even isotonic solutions. The large amounts of glucose in water which were given as a vehicle for nor-epinephrine probably were in retrospect harmful. Actually, nor-epinephrine can be given in smaller volumes of fluid.

DR. MOORE: Dr. Massie, do you think this patient should have been digitalized? If she had, do you believe she would have developed pulmonary edema during the transfusion of whole blood?

DR. EDWARD MASSIE: It would have been worth while to have given her digitalis, though I doubt that it would have accomplished very much because of the other complicating factors.

DR. MOORE: In summary, I believe it is the consensus that the patient had viral epidemic hepatitis of insidious onset, developed progressive hepatic insufficiency, and died of pulmonary edema while she was being treated for the low salt syndrome.

Clinical Diagnosis: Viral epidemic hepatitis with hepatic insufficiency and low salt syndrome.

PATHOLOGIC DISCUSSION

DR. JOHN M. KISSANE: The abdominal cavity at autopsy contained 6,000 ml. of clear, straw-colored fluid with a specific gravity of 1.010. This fluid was fairly well isolated from the tract of the previous paracentesis by fibrous adhesions which contained numerous dilated venous channels. There were also collateral venous channels communicating between the mesocolon and lateral and anterior abdominal walls. The liver weighed 1,830 gm. As shown in Figure 1, its shape was somewhat distorted by the presence of an accessory lobe on the inferior surface and marked reduction in size of the left lobe. The capsule was wrinkled and numerous circumscribed, but not encapsulated, yellowish-tan nodules bulged beneath the capsule. The liver cut with increased resistance. The bulk of the right lobe consisted of collapsed hemorrhagic stroma with raised bands of persisting parenchyma in the peripheral parts of the lobules. (Fig. 2.) Practically all of the secondary and tertiary tributaries of the hepatic veins contained red, firm thrombi. The major hepatic vein contained a few small flecks of gray mural thrombus and there was a small mural thrombus in the vena cava. The portal vein and the splenic veins were patent and not remarkable. The lungs were increased in weight and very moist, subcrepitant and dark red.

DR. DAVID E. SMITH: The most impressive gross finding was that of cirrhosis of a somewhat peculiar pattern, with secondary splenomegaly and collateral venous channels. The most puzzling thing about this cirrhosis was an obvious element of nodular regeneration in what was otherwise a pattern of extreme congestion and centrilobular atrophy.

The first microscopic illustration (Fig. 3) is of one of the hepatic veins, which were thought grossly to contain relatively fresh thrombi. In the lower part of the field there is a large amount of fresh thrombus, but there is also a definitely organized mass adherent to the upper wall of the vein and completely covered by fibrous tissue. It takes many days to several weeks for the inward migration of fibroblasts to organize a thrombus to this degree. The wall of this vein is free of any recognizable inflammatory involvement. Figure 4 shows a vein that is almost occluded by a completely organized thrombus. It would be a conservative estimate that a thrombus so completely organized is at least two months in age. With this establishment of a minimum age of the thrombotic process, it is apparent that these thrombi in this cirrhotic liver were not something which developed terminally or even during the last two admissions to the hospital. Figure 5 illustrates a section of the vena cava and shows a small thrombus that is partially organized by an overlying layer of fibrous tissue. It is noteworthy that the wall of this vein is of normal appearance with no evidence of inflammation. Figure 6 shows a collapsed lobule with a small portal space in which there is fibrosis and proliferation of small bile ducts as well as atrophy and fragmentation of hepatic cords in a manner that can be seen in any very badly damaged liver. The etiology of such damage is not specifically indicated by the histologic pattern, but of course is often seen in virus hepatitis among other diseases. It is noteworthy that there is no evidence of progressive inflammation in these damaged portal spaces or lobules. Figure 7 shows one of the regenerative nodules which were present throughout this liver. It is a nodule of hypertrophied hepatic parenchyma without lobular architecture and is surrounded by fibrous bands. This pattern in the liver is one of extreme congestion and thrombosis of central veins, atrophy of hepatic lobules, regenerative activity without progressive inflammation in the portal spaces and nodules of parenchymatous hypertrophy and regeneration scattered irregularly throughout the liver.

Figure 8 shows the very heavy intra-alveolar precipitate indicative of edema in the lungs. There were a few small scattered foci of hemor-

1 2

FIG. 1. A gross view of the liver showing the pattern of extreme congestion and pale areas of persistent parenchyma. Nodules of hyperplasia are particularly evident under the superior capsule and are about 0.5 cm. in diameter.

FIG. 2. An enlarged view of the cut surface of the liver showing firm, red thrombi in the hepatic veins, increased fibrous tissue about the portal system, and the lobular pattern of dark, broad central zones and yellowish peripheral zones.

rhagic bronchopneumonia that was apparently a terminal development in these lungs, but otherwise the picture was entirely one of severe congestion and edema. The section of the spleen showed characteristic, far advanced chronic passive congestion with thickening of the sinusoidal walls, another evidence that the disturbance in this patient's portal circulation was of at least several months' duration.

In the analysis of this atypical cirrhosis it is possible to discard its classification as any ordinary type of portal cirrhosis on the basis of its gross and microscopic appearance. The factors that require consideration in this case include the history of infectious mononucleosis, the possibility of inoculation or infectious hepatitis, the question of exposure to hepatotoxins, and the possibility that this is the picture of extreme congestion secondary to thrombosis of the hepatic veins or Chiari's disease. The clinical discussion has quite well evaluated the first three of these suggestions. Infectious mononucleosis is apparently not positively proven to lead to cirrhosis. Specific hepatotoxins were certainly not indicated by any positive evidence after careful clinical investigation. If this is an example of inoculation or epidemic viral hepatitis, it is of an unusual, although clearly recognized type, without clinical jaundice even in the terminal phase. Pathologically the picture is not typical of that disease because of the extreme congestion, the thrombi, and the lack of any evidence of progressive inflammation or hepatonecrosis. The absence of any specific indication of these other three factors leaves the question as to whether this change in the liver can be the result of extreme congestion and atrophy secondary to the thrombosis of the hepatic veins. Certainly the lesions in the veins are as old as any other features that can be recognized in these sections.

Chiari's disease was described in 1899, although actually the syndrome had been previously characterized many years before by other workers. It is not a common disease, and there were recently only a few more than seventy cases available in the literature. Almost every pathologic report has been occupied with descriptions of the changes in the vessels without very detailed mention of the changes in the parenchyma of the liver. Several state that the patient had cirrhosis without further description or distinction between the possible types of cirrhosis. In investigating the literature on chronic passive congestion of the liver, however, it can be found that there are experimental examples of extreme induced passive congestion of the liver that lead to destruction of the parenchyma and nodules of regeneration after a long period of time. Such a picture might be considered a very late phase of what we usually call cardiac cirrhosis although it is not seen in most human cases. With the lack of features that we can clearly recognize as indicating any of the other etiologic possibilities in this case, and with the experimental evidence that a picture including extreme congestion, parenchymatous destruction and regenerative hypertrophy can be

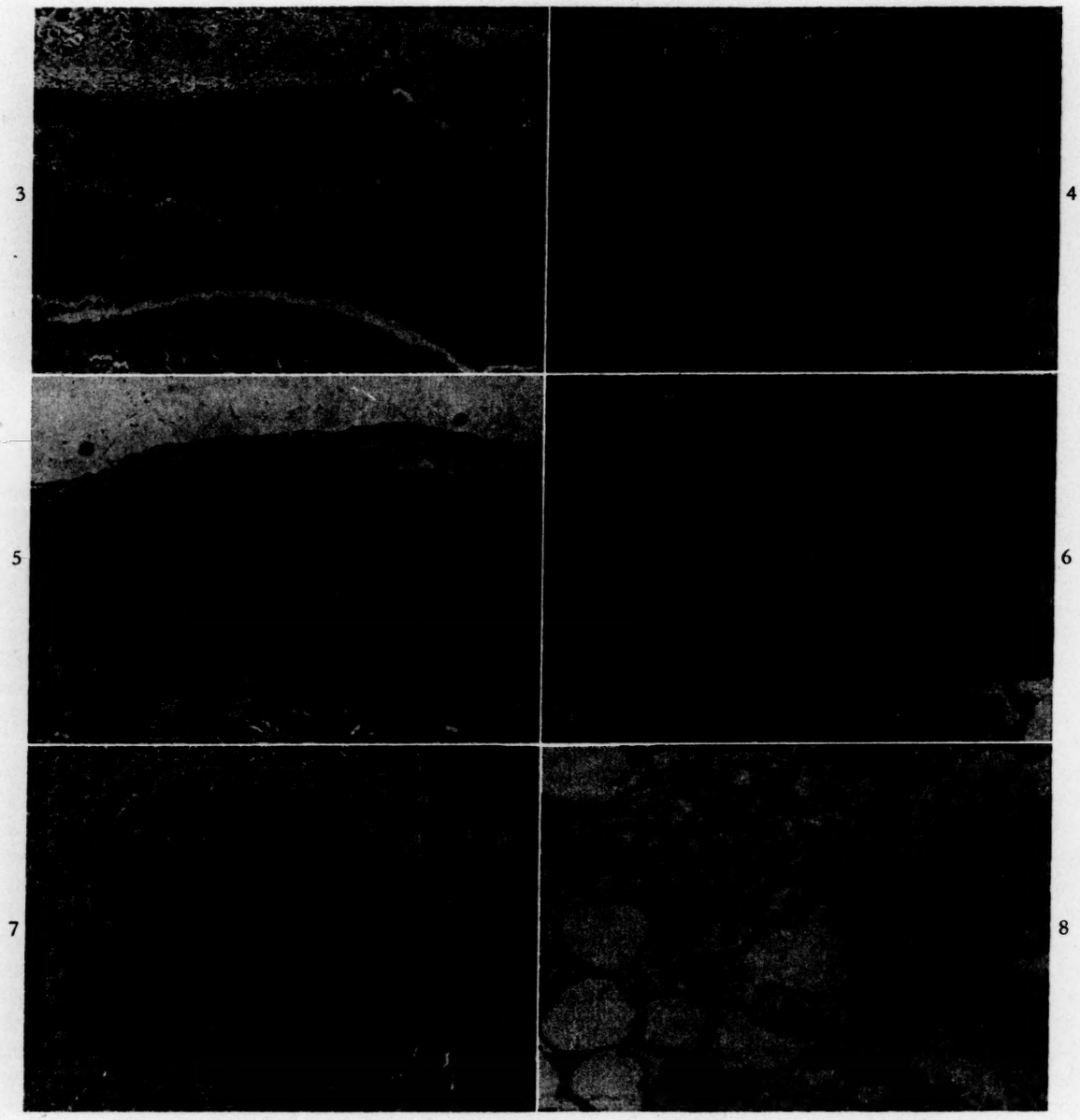

FIG. 3. A section through a hepatic vein with a recent thrombus in the lower portion of the field and an organized thrombus with an overlying capsule of fibrous tissue attached to the upper wall.

FIG. 4. An hepatic vein that is almost completely occluded by an almost completely organized thrombus.

FIG. 5. A small mural thrombus on the wall of the major hepatic vein with no evidence of underlying inflammation or disease of the wall of the vein.

FIG. 6. A section of a collapsed hepatic lobule with a small portal space on the left, irregularly destroyed hepatic cords, proliferated small bile ducts, and great dilatation and congestion of the sinusoids in the region of the hepatic vein to the right.

FIG. 7. A nodule of parenchymatous regeneration in the liver.

FIG. 8. The lung showing the pattern of almost pure congestion and heavy edema. There were a few foci of hemorrhagic bronchopneumonia of very slight extent.

induced in livers by occlusion of the hepatic veins, we have, therefore, come to the conclusion that the changes in the parenchyma of this liver are secondary to the well established old thrombi in the hepatic veins. This is, therefore, a case of Chiari's disease, but giving it such a label does not clarify its etiology.

A variety of etiologies have been suggested for Chiari's disease.* Chiari himself described it as an endophlebitis which he thought was a specific syphilitic vascular lesion of the same nature as Heubner's arteritis of the cerebral arteries. Some of the described cases have been secondary to thrombosis of the vena cava due to invasion by tumor or a number of other causes. Other authors have suggested that the oblique union of the hepatic veins and the vena cava set up eddy currents that give rise to the thrombi. Another theory is that the torsion of the hepatic veins when the individual is in the upright position leads to scarring of the ostia with secondary thrombosis. The reversal of venous flow with inspiration and the lodging of emboli in hepatic veins has been suggested as the etiologic cause. Other things such as fetal interstitial hepatitis, progressive post-natal venous occlusion beyond the normal limits of the ductus venosum have all been suggested as the etiology of Chiari's disease. Cases obviously secondary to lesions in the liver have been described as this syndrome without actually representing primary thrombosis of the hepatic veins. The multiplicity of suggested explanations of the etiology of the so-called primary hepatic venous thrombosis illustrates the extent of our ignorance of its true nature.

It is quite possible that there may have been in the present case some primary inflammatory disease in the liver that gave rise to the thrombi; however, as far as can be seen by examination of the tissue at the time of death there persists no recognizable evidence of such primary hepatic disease. Rather, the thrombi are apparently as old as any of the recognized lesions. All the remaining changes in the liver are of such a nature that they could be secondary to thrombosis of the hepatic veins. We can do nothing more than leave the case at this point. The findings in the remaining viscera did not suggest any other primary disease that might explain the circulatory failure of the last day of this patient's life. The kidneys were histologically normal.

Final Anatomic Diagnoses: Partially organized and recent thrombi in radicles of the hepatic vein, advanced, and small partly organized mural thrombi in the hepatic veins and inferior vena cava; congestive cirrhosis of the liver with nodular regeneration; congestion and edema of the lungs, advanced; bronchopneumonia, slight.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

* Hirsch, H. L. and Manchester, B. Chiari's syndrome. *New England J. Med.*, 235: 507–511, 1946.

Case Reports

Rheumatoid Spondylitis with Carditis*

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Rheumatoid spondylitis is a well recognized clinical entity for which "ankylosing spondylitis" and "Marie-Strümpell arthritis" are commonly used synonyms. However, little is known about the syndrome except its clinical characteristics. Its relationships to rheumatoid arthritis of the peripheral joints as well as to rheumatic fever have been in dispute. Involvement of the heart by rheumatoid spondylitis has been reported but has received little emphasis. The following case of rheumatoid spondylitis, peripheral rheumatoid arthritis and carditis is reported for this reason and because of the interesting questions it raises.

CASE REPORT

W. J., No. 134180, a white man age forty-two years, was admitted to Mills Memorial Hospital for the second time October 17, 1952, complaining of fever, aches and stiffness in various parts of his body, and painful swelling of several joints.

He had been in good general health until September 20, 1952, when a chronic epidermophytosis of both feet became secondarily infected. He was hospitalized October 2 to 12, 1952, and was treated with terramycin orally, aluminum acetate solution compresses and later a mild tar-containing lotion locally to the lesions with good response. For two days during the period of initial hospitalization he had a slight sore throat without fever.

About October 14, 1952, the patient first developed generalized malaise and began to have excessive nocturnal sweats. Within twenty-four hours stiffness and aching in the left shoulder and left side of the neck appeared and in the next few days stiffness in the left elbow. On October 16th sudden pain, swelling and redness appeared in the right knee, with a temperature rise to 102°F.

The review of systems disclosed the following information: His weight had been constant and no previous fever had occurred. He had no headaches and no visual or auditory changes. There had been a two-day mild sore throat about October 2, 1952. There were no cardiorespiratory complaints. He had had a mild diarrhea that had disappeared shortly after oral terramycin medication was stopped. There had been no genitourinary complaints. His skin lesions were much improved and medications had consisted of Burow's solution and a mild, tar-containing lotion topically, terramycin orally, and occasional doses of salicylates and barbiturates orally. He had a normal dietary history, denied the use of tobacco, took only an occasional cocktail and drank coffee moderately.

He had had the usual childhood diseases including measles, mumps and chicken pox. He had been injured in an automobile accident in 1939 with some subsequent back distress diagnosed as "sacroiliac strain." There had been a skin eruption provoked by sensitivity to sulfathiazole ointment in 1940. He denied any other type of illness at any time. There had been no previous joint complaints. He specifically denied rheumatic fever, arthritis and chorea.

Later questioning revealed a story of intermittent, mild to moderate back distress for thirteen years, since the automobile accident in 1939. This had never been incapacitating and had responded to physiotherapy and regulated exercise.

His mother had rheumatic fever at the age of sixteen, with no recurrence. She was living and in good health at the age of sixty-three. His father died at the age of eighty-three of unknown cause. There were no other cases of "rheumatism" or arthritis, or rheumatic fever among his relatives. Gout was specifically denied. The patient was married but childless, and worked as a salesman for an electrical supply house. His working and living habits were temperate.

Physical examination on entry showed an acutely ill, febrile, white man. There was exces-

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sive perspiration on the trunk and extremities, and a drying, crusted eruption covering an area about 2 inches in diameter over the dorsum of each foot. The blood pressure was 130 systolic and 80 diastolic, with the pulse 96 per minute and regular, respirations 20 per minute and temperature 102.4°F. Stiffness, tenderness on palpation and pain on active and passive motion of the left shoulder and right knee were noted. The right knee was swollen and reddened. The head and neck were normal except for moderate muscle spasm in the neck. The trachea was in the midline, the thyroid palpable but not enlarged, and no cervical lymph nodes were palpable. Examination of the chest showed normal respiratory excursions, with the lungs being clear to auscultation and percussion. There were no palpable axillary or inguinal lymph nodes. The heart was not enlarged on physical examination, the rate was 96 per minute and regular, and there were no thrills, murmurs, friction rubs or gallop sounds. The abdomen was normal, and the liver, spleen and kidneys could not be felt; there was no costovertebral angle tenderness to fist percussion. The external genitalia were normal, and digital examination of the rectum revealed normal findings. The prostate was normal in size, shape and consistency, and there was no tenderness. Except for the abnormalities noted above in the joints the extremities were normal, with normal peripheral vessels. No subcutaneous nodules were ever discovered. The neurologic examination showed normal findings.

The patient was treated symptomatically as a case of migratory polyarthritis of unknown cause, for the next month receiving physiotherapy, high protein diet, multiple vitamin preparations, analgesics and an occasional mild barbiturate sedative. During this period he had fever almost daily, occasionally to 101°F. He lost 15 pounds. Stiffness and pain appeared successively in the right wrist, the left knee and the small joints of the right foot, while the right knee continued acutely swollen and tender. There was persistent aching and stiffness in both shoulders, the neck and the interscapular region.

Laboratory examination during this month gave the following results: There were 13.6 gm. of hemoglobin per 100 cc. of blood by the sodium carbonate method, and 5,060,000 red blood cells and 11,700 white cells per cu. mm. of blood, the differential count showing 86 per cent neutrophils and 14 per cent lymphocytes. Urine specific gravity was 1.019, the reaction acid, with negative tests for sugar, albumin and acetone. No microscopic abnormalities were noted in the urine. The packed cell volume was 43, and the sedimentation rate by the Wintrobe method rose from 25 mm. per hour to 45 mm. per hour during the month. Two stool examinations showed no ova, parasites or occult blood, and stool culture showed no colonies of typhoid, salmonella, shigella or other pathogenic organisms. The heterophil antibody test showed no titer, and the agglutination reactions for typhoid, para-typhoid A and B, Brucella, and tularemia were all negative. The fasting blood uric acid was 3.8 mg. per 100 cc. of blood, well within normal limits of the laboratory. Two x-ray examinations of the right knee showed only soft tissue swelling, and a chest x-ray showed normal findings with no evidence of cardiac enlargement. Fluid aspirated from the right knee was slightly turbid, yellowish in color, and sterile on culture. Microscopic examination showed large numbers of white blood cells (principally neutrophils) and a few red blood cells, with no bacteria detectable on the gram-stain smear. The antistreptolysin titer, done twice during this period, was less that 12 Todd units on both determinations. Biopsy of the left latissimus dorsi muscle showed histologically normal muscle tissue. A routine 12-lead electrocardiogram obtained on November 4, 1952, showed sinus tachycardia with a rate of 102 per minute, a P-R interval duration of 0.21 second, normal QRS duration and configuration, and minor non-specific T-wave abnormalities in standard lead I, and unipolar extremity lead aVL.

Evidence of carditis was first clearly detected about the end of this period. There appeared a grade III (Levine) low-pitched rough apical systolic murmur, audible clearly in all body positions at varying heart rates from 80 to 120 per minute. A mid-diastolic summation gallop sound also became audible about this time. On November 15, 1952, a second electrocardiogram (Fig. 1) showed a P-R interval of 0.30 seconds with sinus rhythm, at a rate of 92 per minute. There was some elevation and straightening of the RS-T segments in several of the leads, with a flattened T-wave in unipolar extremity lead aVL.

Cortisone therapy was commenced November 17, 1952, in a dose of 25 mg. orally every six hours. He was also given aspirin in a dose of 4.0 gm. every twenty-four hours. Three days after this medication was started the patient

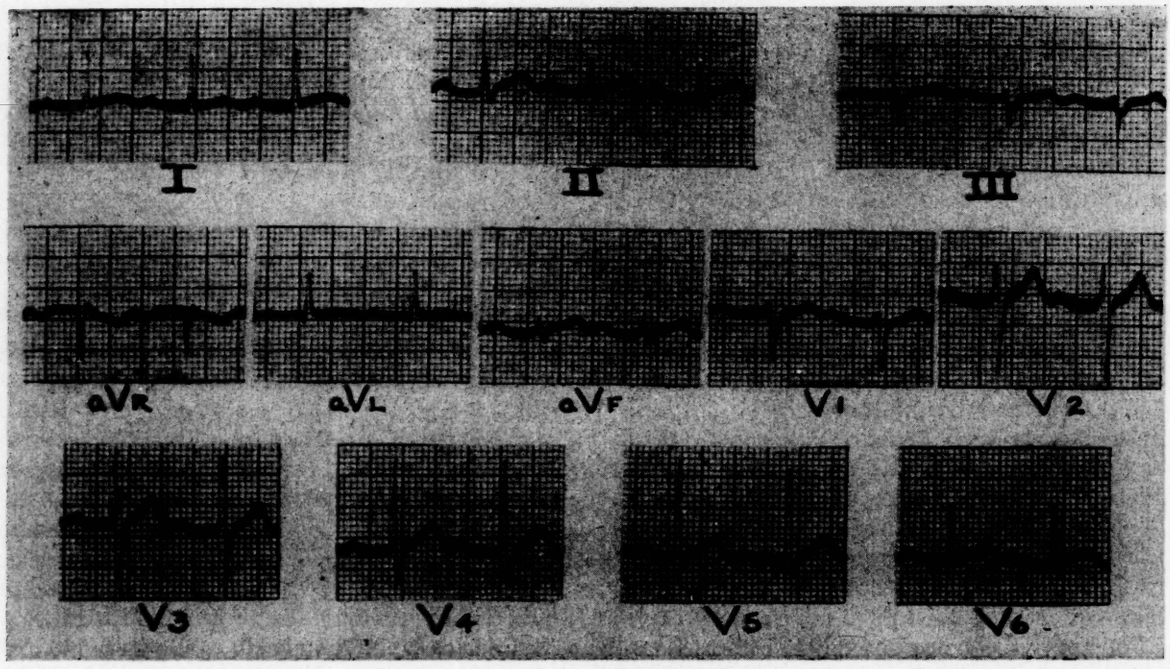

FIG. 1. An electrocardiogram November 15, 1952, taken while the patient showed signs of active arthritis, exhibits prolonged P-R interval, slight elevation and straightening of RS-T segments in leads I, II and V_6, with a low T in aVL.

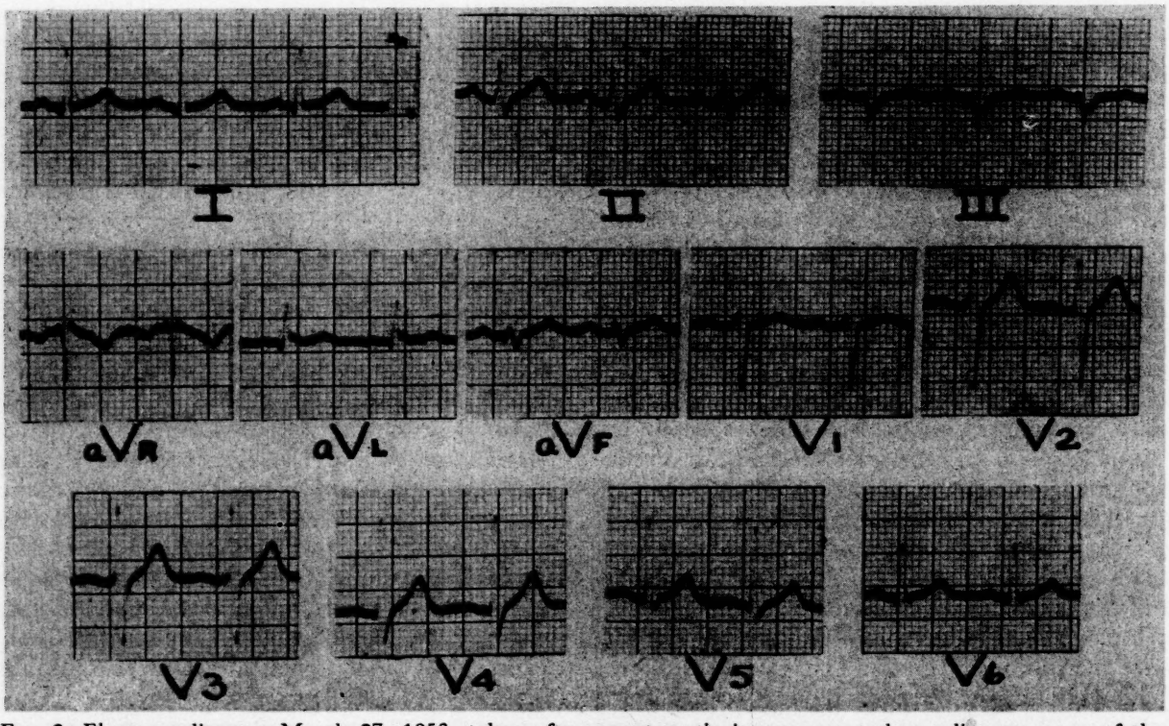

FIG. 2. Electrocardiogram March 27, 1953, taken after symptomatic improvement shows disappearance of the auriculoventricular block, and normally upward concave RS-T segments in leads I, II and V_6, with T wave in aVL of normal amplitude.

began to show marked improvement. His low grade fever and excessive sweating disappeared, his appetite improved, and the pain, tenderness and stiffness in all his joints improved considerably. He was sent home on November 23, 1952.

Subjective improvement continued but was gradual. Stiffness and some swelling remained in the right knee and the small joints of the right foot although all other joints became grossly normal. Some stiffness remained in the neck. The systolic apical murmur and the gallop rhythm persisted unchanged for approximately four weeks, then gradually disappeared and have never recurred. Serial electrocardiograms demonstrated varying but regularly prolonged P-R intervals. On November 29, 1952, the heart rate was 90 per minute and the P-R interval was 0.28 seconds; on January 2, 1953, the heart rate was 90 per minute and the P-R interval was 0.26 seconds. On January 23, 1953, however, with a heart rate of 100 per minute, the P-R interval was 0.18 seconds, within normal limits, and the minor T-wave abnormalities had disappeared. An electrocardiogram taken March 27, 1953, (Fig. 2) was entirely within normal limits, with a P-R interval of 0.18 seconds, sinus rhythm, a heart rate of 100 per minute, and normally upward-concave RS-T segments and normal T-waves throughout.

The patient was gradually allowed up and the cortisone dosage gradually decreased, then stopped by March 1, 1953. Even on a cortisone dosage of 100 mg. per twenty-four hours the sedimentation rate remained at 30 to 40 mm. per hour by the Wintrobe method. As the dose was lowered, pain and stiffness in the back of the neck and shoulders gradually became more severe. Some exacerbation of the swelling and stiffness in the right knee and the small joints of the right foot became evident as well.

An x-ray examination of the complete spine done on March 12, 1953, showed moderately advanced rheumatoid spondylitis. There was generalized osteoporosis of all bony components. A moderate kyphosis was evident and the costovertebral joints showed narrowing, with proliferative changes at their margins. The sacroiliac joints showed marked raggedness and sclerosis, with evidence of destruction of the joint surfaces, typical of the changes regularly found in rheumatoid spondylitis. (Fig. 3.)

The patient was given two courses of x-ray therapy to the spine in March and April, 1953, with marked improvement in the back, neck and shoulder pain and stiffness. Although some stiffness and swelling persisted, the right knee and the right foot gradually improved and the patient's strength increased. The temperature and pulse remained normal, repeated blood counts gave normal values, and the sedimentation rate gradually decreased to a low of 22 mm. per hour on May 8, 1953, by the Wintrobe method. An antistreptolysin titer done on March 29, 1953, was again less than 12 Todd units. With only mild stiffness and puffiness in the right knee, and some mild stiffness in the back and neck, the patient returned to his former occupation on August 1, 1953. No evidence of recurrence of the carditis was ever detected.

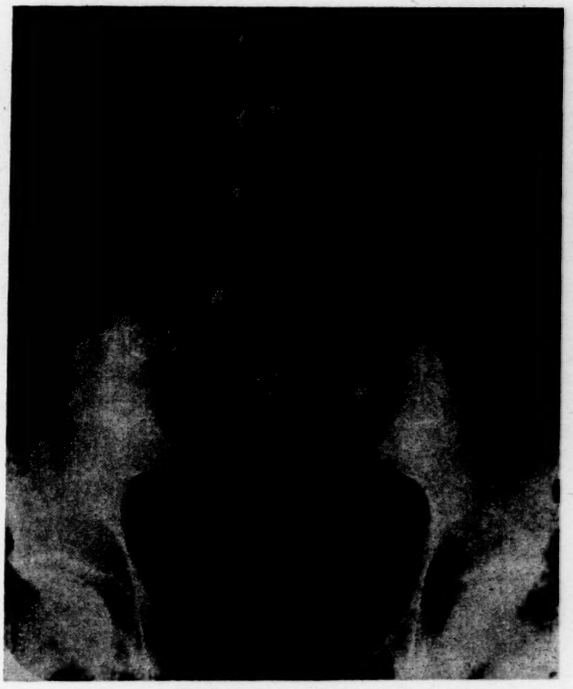

FIG. 3. X-ray of lumbosacral spine taken March 12, 1953, showing raggedness and sclerosis of the sacroiliac joints. Other changes equally characteristic of rheumatoid spondylitis were demonstrable in oblique films.

In retrospect it seems clear that the patient had a smoldering rheumatoid spondylitis for years, with an acute exacerbation accompanied by arthritis of the peripheral joints and carditis. Treatment with cortisone suppressed all signs of activity of the disease process except the abnormal sedimentation rate, and evidence of carditis gradually cleared. An exacerbation of the symptoms of spondylitis followed cessation of cortisone therapy but these apparently

responded to heavy doses of x-ray therapy to the spine.

COMMENT

The occurrence of arthritis of the peripheral joints in association with rheumatoid spondylitis is a commonly observed phenomenon, occurring in approximately 25 per cent of cases. The peripheral arthropathy displays all the characteristics of rheumatoid arthritis.[1] This association is cited as an argument supporting the belief that rheumatoid spondylitis is simply rheumatoid arthritis involving the spine.[2] Another argument advanced to support this contention is that in both processes there are signs of systemic disease in the form of an elevated sedimentation rate, fever and often weight loss. It has been reported that the pathologic changes in the diarthrodial joints of the spine during the active phases of rheumatoid spondylitis resemble those found in rheumatoid arthritis of the peripheral joints.[3] Iritis and obliterative pericarditis are complications found in rheumatoid arthritis of the spine as well as with rheumatoid arthritis of the peripheral joints.[4]

Many disagree with the idea that these two syndromes are essentially identical, however. European workers in particular deny the identity of the two processes and support their contention with some striking facts. The sex incidence of the two is quite different; 90 per cent of patients with rheumatoid spondylitis are males whereas rheumatoid arthritis of the peripheral joints occurs more commonly in females. The calcification of the ligaments found so characteristically in rheumatoid spondylitis does not occur in rheumatoid arthritis of the peripheral joints. Gold therapy is ineffective in rheumatoid spondylitis but often helpful in rheumatoid arthritis of the peripheral joints. X-ray therapy is beneficial in a large percentage of the cases of rheumatoid spondylitis but useless in peripheral joint disease.[5] Subcutaneous nodules characteristic of rheumatoid arthritis of the peripheral joints do not occur in cases of rheumatoid spondylitis unless peripheral joint involvement is also present. Sensitized sheep erythrocytes are often agglutinated by serum from patients with rheumatoid arthritis but not by serum from cases of rheumatoid spondylitis.[6] Additional, less obvious differences have been cited so that the question cannot be considered as settled.[7,8]

Some controversy also exists regarding the relationship between rheumatoid arthritis and rheumatic fever. Clinically, they are sometimes difficult to distinguish, leading some to believe that the two syndromes are simply different manifestations of the same process.[9,10] It has been suggested that certain types of rheumatic fever may produce a chronic rheumatic joint disease distinct from, although closely resembling, rheumatoid arthritis.[11,12] The histopathologic characteristics of the subcutaneous nodules that occur in rheumatic fever and rheumatoid arthritis are considered by some authors to be the same and that any differences between the two can be accounted for by differences in the ages of the patients and the duration of illness in the individual case.[13,14] Others state categorically that the subcutaneous nodules of rheumatic fever are as different from those of rheumatoid arthritis in their pathologic features as are the lesions of tuberculosis from those of syphilis.[15] Dawson and Tyson in America and Klinge in Europe have emphasized the similarities between the two diseases. A "rheumatic state" is held responsible for both diseases, and the age of the patient and the duration of the process are the determining features in the resulting clinical picture: In childhood and youth, when rheumatic fever is most common, joint involvement is usually relatively mild, whereas cardiac complications are often severe and chorea may occur; in adults who are affected, joint disease is relatively severe, heart damage mild and chorea rare.[16,17] Recently, however, the immunologic differences between the two have been studied and reemphasized.[18]

Opinions are also varied on the subject of cardiac involvement in rheumatoid arthritis. In recent years postmortem studies on cases of rheumatoid arthritis have indicated that heart disease occurs in a higher percentage of patients with this disease than in the general population examined at the autopsy table. The heart disease found in most instances is indistinguishable from rheumatic heart disease. The reported incidence of cardiac disease in such studies has varied from 7 to 65 per cent, with several authors reporting more than 30 per cent incidence of such findings.[19–22] To explain these data the following possibilities have been suggested: (1) that rheumatic fever and rheumatoid arthritis are actually fundamentally the same disease process; (2) that rheumatoid arthritis may produce a form of heart disease indistinguishable from rheumatic heart disease;

(3) that patients with rheumatic heart disease and rheumatoid arthritis may coincidentally have two entirely unrelated diseases.[23]

In striking contrast to the results of these postmortem studies, most clinical studies with rheumatoid arthritis have shown little or no greater incidence of heart disease among these patients than among the general population. Sokoloff has pointed out that the morphologic criteria for the diagnosis of rheumatic heart disease at autopsy vary, and that some of the cases so diagnosed in the reported series actually had only minimal evidence of heart disease.[24] This factor may help explain the discrepancy between postmortem and clinical findings concerning the incidence of rheumatic heart disease in patients with rheumatoid arthritis. Quite likely the clinical studies give falsely low results because of the well recognized difficulty of detecting minor pathologic cardiac changes in the living patient. The factor of selection has been suggested as introducing error into the autopsy percentages, tending to result in falsely high incidence of rheumatic heart disease in cases of rheumatoid arthritis.[25]

Some authors have described a type of heart disease specifically related to rheumatoid arthritis, termed "rheumatoid heart disease," and characterized by foci of granulomatous inflammation similar to that found in the subcutaneous nodules of rheumatoid arthritis.[24,26–28] The frequent occurrence of fibrous obliterative pericarditis accompanying rheumatoid arthritis has been re-emphasized recently.[24] A case of chronic adhesive pericarditis associated with rheumatoid arthritis has been described in which pericardiectomy resulted in symptomatic improvement.[29]

Cardiac involvement in rheumatoid spondylitis has been rarely noted in the literature until recently. In a monograph, Krebs and Wurms stated that the heart is often attacked by the disease, especially in those cases occurring after acute polyarthritis. However, Volhard does not mention cardiac complications, nor are they mentioned in Comroe's book.[30] Herrick and Tyson noted that endocarditis or iritis may occur in an occasional case of rheumatoid spondylitis.[31] Fischer found valvular heart disease in eleven of his one hundred cases and suggested a relationship between acute rheumatic fever and rheumatoid spondylitis. Krebs and Vontz describe a case of rheumatoid spondylitis which followed acute rheumatic fever, with involvement of the aortic valve.[32] Bauer and his associates described several cases of aortitis and aortic valvulitis in individuals with rheumatoid spondylitis, 75 per cent of whom also showed rheumatoid arthritis of the peripheral joints.[33] Four of seven cases of rheumatoid spondylitis described by Edstrom exhibited organic heart disease presumably due to rheumatic fever.[34] Fraser reported two cases of rheumatoid spondylitis in sisters, one of whom had typical rheumatic mitral stenosis.[35] Astrup has reported a case of rheumatoid spondylitis in a man with the electrocardiographic finding of intermittent left bundle branch block; no other cause of heart disease could be detected in this patient.[36] Rosenberg and his associates give a clinical resumé of a case of rheumatoid spondylitis with progressive cardiac disease, shown at postmortem to be morphologically identical with rheumatic heart disease.[13] A similar case is reviewed by Young and Schwedel, with electrocardiograms showing auricular fibrillation.[20] Sokolow and Snell comment on six cases of "Marie-Strümpell arthritis," all of whom showed cardiac findings which the authors took to indicate the coincidental occurrence of rheumatic fever and rheumatoid spondylitis.[37]

The most extensive studies concerning the incidence of cardiac involvement in rheumatoid spondylitis have been published by Bernstein.[30,38] This author found that of 352 patients with rheumatoid spondylitis, forty-two (11.9 per cent) showed clinical or electrocardiographic signs of heart disease evidently rheumatic in origin. Of 190 patients in this group in whom electrocardiograms were taken, twenty-nine showed prolonged P-R intervals, including two with second degree and three with complete auriculoventricular block. The majority of these patients with abnormal electrocardiographic findings exhibited no other cause of heart disease. Peripheral joint involvement was twice as common in those with abnormal hearts. This author believed that the heart disease was produced by coincidentally occurring rheumatic fever. She pointed out, however, that the carditis seen in these patients tended to be much milder in degree than that commonly occurring in cases of acute rheumatic fever in childhood and adolescence. Many patients suffered no evident ill effects of the heart disease they manifested. While this relatively benign course was in part due to the restriction of activity imposed by the arthritis, the author concluded

that the carditis accompanying rheumatoid spondylitis was of essentially mild nature, with a relatively good prognosis, even though the pathologic process seemed identical with that of rheumatic fever in other respects.

The same generalization appears to be true for the patient reported here. Although unmistakable signs of cardiac involvement were demonstrated, at no time did the patient have symptoms referable to the heart or circulatory system. All signs of cardiac involvement disappeared within a few weeks, leaving no demonstrable evidence of heart disease. Although the pathologic process causing rheumatoid spondylitis appears occasionally to produce heart disease, the heart damage has usually been relatively mild. Whether the changes in the heart noted in rheumatic fever, rheumatoid arthritis of the peripheral joints and rheumatoid spondylitis are actually identical in morphology and pathogenesis, or only strikingly similar, cannot be determined on the basis of present knowledge, and the exact relationship between these syndromes remains unclear.

SUMMARY AND CONCLUSIONS

A case of active arthritis of the peripheral joints and of the spine with the clinical characteristics of rheumatoid arthritis and rheumatoid spondylitis in a man forty-two years old is reported. During an acute phase of the disease signs of carditis appeared without producing symptoms of heart disease. Later the signs of carditis completely disappeared without demonstrable residua. The significance of these observations is discussed, and it is concluded that carditis associated with rheumatoid spondylitis tends to be mild, with a relatively good prognosis.

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Suppression of the Manifestations of Gout with Continuous Cortisone Therapy*

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GOUT can frequently be controlled satisfactorily with the older remedies, such as colchicine, salicylates, diet, etc., but one encounters cases that are not amenable to any of these measures, used singly or in combination. In such instances the physician may become a helpless observer as the progress of the disease eventually results in deformities and other complications.

Although corticotropin (ACTH) and cortisone have proved effective agents in the control of the acute manifestations of various forms of arthritis, cessation of their use is usually followed by recurrence. With a disease such as gout, in which there can be severe and frequent disability and ultimate permanent changes, the use of one of these preparations more or less continuously might be one solution to the problem of treatment. Now that cortisone has become available at a relatively low cost, such a plan becomes financially feasible, so that the remaining consideration involves possible deleterious effects of continued cortisone therapy. That this drug can be effectively employed for a prolonged period is indicated by the following case report.

Course Prior to Use of Cortisone. A. G. (No. 24572), a forty-one year old white bus driver, was admitted to the Veterans Administration Hospital, New Orleans, on April 22, 1950, complaining of a painful, swollen left ankle. Since 1944 he had had recurrent attacks of acute joint symptoms, which predominantly affected the wrists, elbows, knees, ankles, feet and great toes, either in a monarticular or polyarthritic fashion. The joints would become acutely swollen, erythematous and extremely painful and tender. These episodes would last as long as three to six weeks and were, in the beginning, separated by intervals of at least several months' duration during which the patient remained well. On the evening before admission he began to experience pain and swelling in the left ankle. This became progressively more severe so that he was forced to use crutches when admitted to the hospital.

There was no family history of gout or other arthritides. System review disclosed a history of seasonal coryza consistent with ragweed hay fever.

Physical examination revealed a mildly obese individual who used crutches because of an exquisitely painful left ankle. There was marked tenderness of that part, especially over the medial aspect, and a moderate amount of periarticular soft tissue swelling. On the medial aspect of the right ring finger there was a 1½ cm. non-tender, firm, subcutaneous nodule. A similar lesion was located on the right thumb. The temperature and blood pressure were normal.

The serum uric acid was 11.2 mg. per cent and the BUN 19 mg. per cent. Electrocardiogram was definitely abnormal, there being evidence of delayed intraventricular conduction. Complete blood count, urinalysis, radiographic studies of the skeletal system, a roentgenogram of the chest and an erect film of the abdomen were normal.

Shortly after admission the patient was placed on colchicine, gr. 1/100, given at hourly intervals. After eighteen doses he began to experience relief but the medication was continued until a total of twenty-four tablets had been administered. The joint symptoms continued to subside so that twenty-four hours after cessation of therapy the patient was completely asymptomatic. A diagnosis of gout was felt warranted. The patient was discharged from the hospital on April 28, 1950, with instructions to observe a low purine diet, take 100 gr. of sodium salicylate daily for prophylaxis and to use colchicine should difficulty recur despite these measures.

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During the course of the illness the episodes of arthritis gradually increased in frequency so that the patient began having one attack after another. Pain-free intervals of longer than one week became unusual. Relief from an attack could consistently be obtained with colchicine, six to eight gr. 1/120 tablets taken at hourly intervals. The frequent use of that drug, however, caused such a severe gastroenteritis that it was debatable to the patient which was worse, gout or colchicine, and he stated that he had strongly contemplated committing suicide on occasion. He lost much time from work. The prophylactic use of various doses of colchicine was tried but proved completely ineffective in preventing attacks.

The patient was again admitted to the hospital on May 7, 1951, with mild arthritic symptoms of short duration involving the left ankle. Other than differences in the degree of joint findings, physical examination disclosed no significant changes since the previously mentioned hospitalization. During his hospital stay the difficulty with the left ankle became worse, and a severe attack involving the right ankle developed.

Course on Cortisone Therapy. Because of the distressing situation cortisone was begun on May 15, 1951, with an initial daily amount of 300 mg. Within twenty-four hours after the first dose there was 50 per cent subjective improvement and a marked increase in the general sense of well-being, but no significant objective joint changes. Over the next five-day period, however, there was gradual complete disappearance of all signs and symptoms. The patient was discharged from the hospital on July 25, 1951, at which time he was taking 150 mg. of cortisone orally daily.

Since then he has been seen at weekly intervals, and various adjustments have been made in the cortisone dosage. Initially, even with 150 mg. daily, he continued to have recurrent acute joint symptoms at intervals of about one week. These were comparatively mild, responded to non-toxic amounts of colchicine, and were never of more than a few days' duration. The patient was pleased with these results but even these episodes gradually diminished in severity and frequency over a period of time. Concomitantly, the dosage of cortisone was reduced so that by August 15, 1951, a daily amount of 50 mg., given in two divided portions, was being administered. Since that time the program has not been changed. There have been only episodes of mild erythema, frequently without any, or at most, only slight discomfort, at one- to two-month intervals: and these have usually subsided spontaneously in less than twenty-four hours. Occasionally, supplementary colchicine has been required but rarely have more than three or four gr. 1/120 tablets been necessary. This situation is in marked contrast to the previous one of excruciating attacks occurring at weekly intervals. The nodules on the right ring finger and thumb have, to our surprise, gradually and completely disappeared, and the patient has noted that his hay fever has been unusually mild during the two rag-weed pollinating seasons that have ensued since institution of hormonal therapy. There has been no evidence whatsoever of cortisone toxicity as determined clinically and by appropriate laboratory studies. The serum uric acid has remained unaltered, ranging between 7 and 10 mg. per cent.

At the time of this writing the patient has been taking cortisone daily for twenty-two months—50 mg. per day during most of this period. His mental attitude seems excellent. He has not lost a single day's work because of illness. It is planned to maintain the current regimen indefinitely, or until some alteration in the status warrants a different approach.

COMMENTS

The clinical picture of recurrent episodes of acute arthritis separated by progressively shorter intervals, during which the patient remained well, coupled with an excess of uric acid in the serum and a rapid response of acute symptoms to colchicine, is believed to be reasonable evidence of the presence of gout. Colchicine, although effective in terminating the acute attacks, did nothing to prevent them and produced symptoms which were almost as disabling as the gout. Another agent was therefore needed.

Although Gutman[1] found the use of corticotropin useful in the termination of acute attacks of gout, he believed it was neither feasible nor desirable as a prophylactic. The writer's experience with cortisone in this single example was more favorable. It is apparent that this individual, whose disease was pursuing a progressive, relentless course despite the use of the older tried remedies, was transformed from an anguished, disabled person to a well adjusted

useful citizen by the long-term administration of non-toxic amounts of cortisone.

The disappearance of the nodules (which were presumably tophi) from the fingers, while the serum uric acid level remained elevated and unaltered, favors the concept that the solid phase of the miscible uric acid pool can be altered by uricosuric agents without apparent change in the concentration of circulating urate.[2]

The gradual decrease in the dosage of cortisone required to suppress the clinical manifestations of gout is not easily explained. The basic metabolic defect producing the hyperuricemia certainly remains unaltered. In any event, an initially unsatisfactory response should not necessarily preclude the use of this medication for, with prolonged administration, a more desirable effect might gradually be forthcoming.

Even though this patient with gout was markedly benefited by the administration of cortisone, it is to be emphasized that the process in many other cases is too mild to require the use of specific agents or can be satisfactorily controlled with the tried standard measures. such as colchicine, aspirin and diet. It seems that colchicine should remain the drug of choice in our present state of knowledge, hormonal therapy being reserved for the cases not amenable to other methods of treatment. When such a situation arises, the continuous use of cortisone in the smallest effective dosage deserves consideration. Careful observations are, of course, then essential to detect any deleterious effects of this agent.

SUMMARY

Suppression of acute arthritic attacks and mobilization of solid, presumably tophaceous, deposits in a patient with gout by the prolonged daily administration of cortisone is described. Increasing effectiveness of the drug with the passage of time was observed.

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Nocardiosis*

Report of a Fatal Case

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THE first human case of actinomycosis due to an aerobic, acid-fast actinomycete was described by Eppinger[1] in 1890. Since then sixty-two cases of nocardiosis have been reported in the literature. Cruz and Clancy[2] summarized the pertinent features of forty-three of these and added a case of their own. Eighteen more cases[3–17] may be added to those reviewed by Cruz.

With few exceptions[8,15,18–21] the papers on nocardiosis have been reports of individual cases. The prevalence of such single case reports and the small number of total known cases would make it appear that nocardiosis is a very rare disease. However, the frequency with which the diagnosis of this chronic illness is made only at necropsy or in the terminal stage of the disease would suggest that many cases may never have been recognized. It is also striking that the disease was almost always fatal prior to 1944, and that there is an increase in reported recoveries since the introduction of apparently effective chemotherapeutic and antibiotic agents. Early clinical and microbiologic recognition of this disease becomes all the more important when means of successful therapy are becoming available. Therefore, we are reporting a case of fatal nocardiosis to draw attention to the correlation of its clinical and laboratory aspects.

CASE REPORT

The patient, E. F., a thirty-five year old white male, came to our attention two weeks prior to death when he was presented to a medical staff conference on November 14, 1951, as a diagnostic problem. Table 1 will serve to illustrate the various manifestations of his disease, as well as the diagnostic procedures and therapeutic attempts over a period of sixteen months.

The history prior to August, 1950, was noncontributory. On that date the patient noted a painful swelling in the right buttock. There was no known injury or abrasion. His private physician made the diagnosis of a perianal abscess which was incised and drained, and appeared to heal well. Smear or culture of the pus was not performed. The leukocyte count was 15,000.

About two months later the swelling recurred. The patient felt well otherwise and had no fever. He was hospitalized, the abscess was again drained and a biopsy was also obtained. Culture of the pus was reported as showing gram-positive cocci. Histopathologic examination of the abscess wall revealed granulation tissue. Bacteria and fungi were searched for but none were found. X-ray of the chest showed an increased density over the right middle lobe, suggesting pneumonitis. The patient was treated with penicillin and made an uneventful recovery. He was advised to return for follow-up chest examination but he failed to do so.

The patient returned to work and was apparently well until May, 1951. At that time he fainted suddenly while at work and his fellow workers noted twitching movements of the extremities. When seen by a physician on the same day he had regained consciousness. The only abnormality reported was an elevation of blood pressure to 160/100. It was also noted that a weight loss of 35 pounds had occurred since November, 1950. Following this episode the patient developed severe frontal headaches. About two weeks later he noticed swelling of the right anterior chest wall. He was hospitalized in June, 1951. Pertinent findings at that time included nuchal rigidity, left hemiparesis, papilledema and elevated spinal fluid pressure with normal cell count. The swelling of the anterior

* From The Arthritis Research Unit, and the Medical and Surgical Services, Veterans Administration Hospital, Washington, D. C. Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

TABLE 1
SUMMARY OF CASE

Date	Symptoms	Diagnoses	Temp.	WBC	Spinal Fluid Cell Count	Microbiological Studies							Biopsy Report	Therapy
						Specimen	Smear		Culture for			Guinea Pig		
							Gram	AF*	Bact.	AFB†	Fungi			
August 1950		Perianal abscess	Normal	15,000										Incision and drainage
November 1950		Perianal abscess; pneumonitis ?	Normal	12,000		Pus			Gram positive cocci				Granulation tissue: no bacteria; no fungi	Incision; drainage; penicillin
Dec. 1950 to Apr. 1951	Weight loss 35 lb.													
May 1951	Syncope, headache, swelling on chest wall		Normal											
June	Headache Swelling of right chest wall	Brain abscess Abscess of right chest wall	Normal	12,000		Pus from chest wall abscess	0	0						Penicillin; chloramphenicol
July		Abscess left frontal lobe; abscess chest wall involving ribs, pleura, rt. middle lobe	102°F.	15,900	9	Blood			0				Abscess wall: no tubercles; no caseation necrosis	Craniotomy; penicillin; chloramphenicol
				13,400	3	Brain absc.	0		0					
	Improvement then return of increased spinal fluid pressure				4	Ch. w. absc.	0	0	0	0		0		
August			101°F.	17,700		Blood			0					Penicillin; chloramphenicol
				27,000		Blood			0					
				39,000		Blood			0					
						Chest wall abscess	0		0					
							0	0	0	0		0		
September		6 abscesses right frontal lobe	Normal after 9/12	10,300	238	Blood			Staph.				Abscess wall: no tubercles	Craniotomy; penicillin; chloramphenicol; terramycin
					135	Brain absc.	0		Staph.					
	Improvement; accumulation of fluid under post-op. flap					Fluid rt. temp. reg.	0		0					
						Spinal fl.	0		0		0			
5	Convulsions		102°F.	25,000	8	Fluid right temp. region	0		0					None 10/3 to 10/19 Terramycin
October 19					8		0		?*					
							0		Anaerob. diphth.					
5	Increasing spinal fluid pressure		102°F.	19,600	11	Spinal fl.	0	0	0	0	0			Aureomycin to 11/14
19				35,000		Ch. w. absc.	?	(+)	0	0	Nocardia asteroides			Pen. SM. Gantrisin
Nov. 28		Died		39,000										Sulfadiazine
						Ch. w. absc.	?	(+)			N. asteroides			
						Brain	+	(+)			N. asteroides			
						Subculture of ? cult. of 10/19*					N. asteroides			

(+) = weakly acid-fast organisms.
*AF = acid-fast.
†AFB = acid-fast bacille.

chest wall was fluctuant. The leukocyte count was 23,900. There was no fever. Pus was aspirated from the abscess of the right chest wall and examined by cell block and smear. These studies were reported as: "No malignant cells, no amebae, no organisms of any diagnostic significance." The patient was placed on penicillin and chloramphenicol therapy. He was transferred to the Veterans Administration Hospital, Washington, D. C. in July, 1951, with the diagnosis of "brain abscess, etiology undetermined."

At the time of admission neurologic examination and ventriculogram indicated a space-occupying lesion in the left frontal lobe. The diagnosis of a brain abscess was suspected because of the history of multiple abscesses in various other locations, even though fever had been absent throughout the entire course of the illness. Craniotomy revealed a large thick-walled abscess in the posterior third of the left frontal lobe. The abscess was dissected out intact and found to contain thick yellow pus. The pus and the abscess wall were studied extensively but no information regarding the etiologic agent was obtained. Chest x-rays again revealed abnormalities in the right chest which were interpreted as anterior chest wall abscess involving the adjacent ribs and extending into the anterior pleural cavity with middle lobe inflammatory reaction. Following the craniotomy fever was noted for the first time. This gradually subsided and the patient showed improvement during the ensuing six weeks. During this period repeated blood cultures and cultures of the pus from the chest wall were reported as negative.

Toward the end of August the intracranial pressure again rose and localizing signs indicated a lesion in the right frontal lobe. Craniotomy was performed on September 7th and a group of six thin-walled abscesses was encountered and removed. After the operation the patient presented the picture of a unilateral lobotomy with passiveness and lack of concern. Intelligence did not appear grossly impaired. The postoperative course was complicated by accumulation of fluid beneath the flap, which consisted at first of serosanguineous fluid and later changed to thick, gray, purulent material. All studies of this fluid as well as the pus from the brain abscesses, the spinal fluid and blood continued to be uninformative. A staphylococcus found in one of the blood cultures and in one of the cultures from the brain abscess was difficult to accept as the etiologic agent in view of the entire clinical course. In October the patient had a generalized convulsion and following this his course was steadily downhill.

On October 19th purulent material was again obtained from the right temporal region. This was sent to two different laboratories for study. Laboratory A noted "Unidentifiable filamentous material" in one broth culture. Subculture of this was forwarded to a mycology laboratory where it was reported as: "Inoculated media negative for pathogenic fungi." Laboratory B reported on November 9th that an anaerobic diphtheroid had been grown from the pus. The significance of this was not clear since diphtheroids are found as laboratory and skin contaminants. However, in the light of later findings we must consider that this diphtheroid may have represented the etiologic agent.

At the medical staff conference on November 14, 1951, the problem as presented was that of a patient who for the past sixteen months had developed multiple abscesses involving the subcutaneous tissues, brain and possibly the ribs, pleura and lungs, and in whom the etiology of the illness was still obscure. The consensus was that the patient had a systemic fungus disease rather than a bacterial infection and that actinomycosis was a strong possibility. It was noteworthy that none of the abscesses developed a sinus tract, which would be rather uncommon in actinomycosis due to Actinomyces bovis. Review of the patient's treatment indicated that he had had several courses of penicillin, chloramphenicol and terramycin therapy, and at the time of conference he was receiving aureomycin. Even though this drug does not have marked fungicidal action, it was decided to discontinue it and after an interval of four days to make another attempt to find the etiologic agent. The chest wall abscess was chosen as the site for study.

On November 19th thick, grayish purulent material was aspirated from the abscess and inoculated on a variety of culture media, and incubated aerobically and anaerobically, under reduced oxygen tension, and at room and incubator temperature. The media used were pancreatic digest agar[22] enriched with 20 per cent of ascitic fluid, pancreatic digest blood agar, Sabouraud's glucose agar and fluid thioglycollate medium enriched with rabbit blood. A gram-stained smear of the pus showed gram-positive fragments which could not be definitely

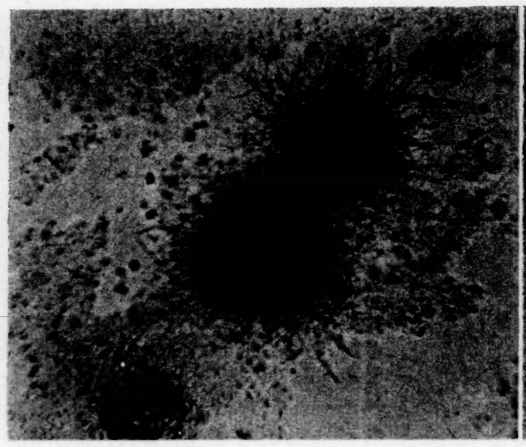

FIG. 1. Colonies of Nocardia asteroides; forty-eight hours' incubation; × 100.

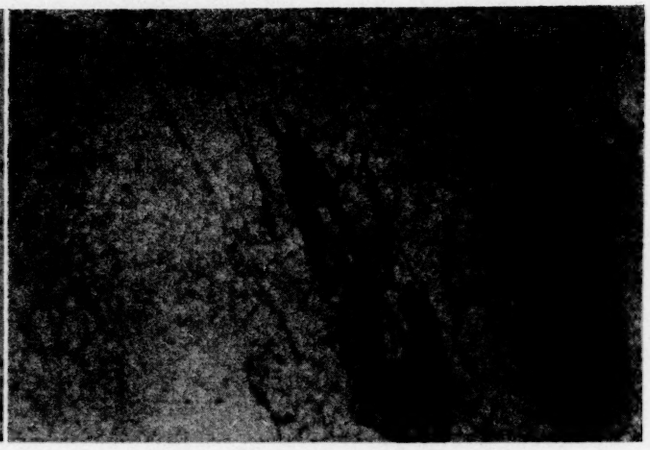

FIG. 2. Pus from chest wall abscess; × 1360; modified acid-fast stain.

identified as bacteria or mycelia. Routine acid-fast stains revealed no organisms. Nocardiosis was being considered by us on clinical grounds, and the variability of acid-fastness of this aerobic actinomycete was recalled. The original acid-fast stain was therefore completely decolorized and restained with Kinyoun stain, but this time 1 per cent aqueous sulfuric acid was used for decolorization instead of the customary acid alcohol. Beaded, acid-fast filaments were then readily demonstrable. After forty-eight hours innumerable microscopic, star-like colonies had appeared on all the solid media, regardless of the method of incubation. In another twenty-four hours these developed into macroscopically visible white colonies. (Figs. 1 and 2.)

The organism seen on smear and grown on culture was identified as Nocardia asteroides. The identification was confirmed by Dr. C. W. Emmons, Principal Mycologist, National Institutes of Health, whose help in this problem was most valuable to us.

Immediately after the material for culture had been obtained treatment with gantrisin, penicillin and streptomycin was started. As soon as studies revealed the presence of Nocardia asteroides, sulfadiazine was added to the therapy. However, the patient continued to lose ground and died on November 28, 1951.

Necropsy. The abscess of the chest wall extended along the fascial planes. Both pleural cavities were uninvolved. In the right lung there was a small area of congestion and atelectasis but no abscesses were found. The brain revealed multiple abscesses in the frontal, parietal and occipital lobes, varying in diameter from a few millimeters to 3 cm. Smears stained with gram stain and with modified acid-fast stain, and cultures from a brain lesion and the chest wall abscess showed Nocardia asteroides.

COMMENT

Clinical Features of Nocardiosis. Because of the hematogenous spread of the infecting organism almost all organs have been affected in nocardiosis. There is a definite predilection, however, for the lungs, brain and subcutaneous tissues. Abscesses in various locations are frequently encountered. Draining sinuses may develop but are not as common as in actinomycosis due to Actinomyces bovis. There is a tendency to remissions and exacerbations. Some patients have remained clinically asymptomatic for as long as eleven months.[23] Fever need not be present in spite of active disease. Many patients show marked leukocytosis with counts up to 50,000.[19] This might be a helpful diagnostic finding if tuberculosis or neoplasm are considered as differential diagnoses. (Fig. 3.)

It is difficult to say whether nocardia infections are as rare as would appear from the scarcity of cases reported in the literature. Tucker and Hirsch[8] emphasized that nocardia grows readily on culture media, yet in two of their own three cases the diagnosis was made only at necropsy. This is a common occurrence. In only fourteen of the thirty-eight fatal cases reported in the literature was the diagnosis established during life and most of these were recognized only shortly before death. The discrepancy between the ease of cultivation of the causative organism and the failure to establish an early

diagnosis is disconcerting and deserves further comment. It may be related (1) to the frequency of brain abscesses in this disease, (2) to overwhelming and therefore easily demonstrable terminal spread of the infection or (3) possibly to failure to suspect the disease on clinical grounds and to search for and recognize the organism early in the disease.

Brain Involvement. The high mortality and difficulty in diagnosis may be related to the frequency of brain involvement, inasmuch as symptoms may develop late in the illness if silent areas are involved. Review of the literature shows that none of the patients who have recovered had demonstrable involvement of the brain or spinal cord. Eckhardt and Pilcher[12] in particular have pointed out the paucity of findings on physical examination in their patient with solitary brain abscess, who developed acute symptoms apparently related to rupture of a thick-walled chronic abscess. This patient had no fever in spite of an obviously active infectious process. Fever was also absent in the fatal case reported by Kaufman and Prieto.[16] In the patient described in this paper fever did not occur until late in the disease.

Extension of Infection. Glover et al.[24] report that many negative cultures were obtained from the clear pleural fluid of one of their patients. However, when the pleural fluid became purulent numerous colonies of Nocardia asteroides appeared on the culture media and subsequently they were demonstrable repeatedly. Such an observation could be related to sudden, overwhelming extension of the infectious process.

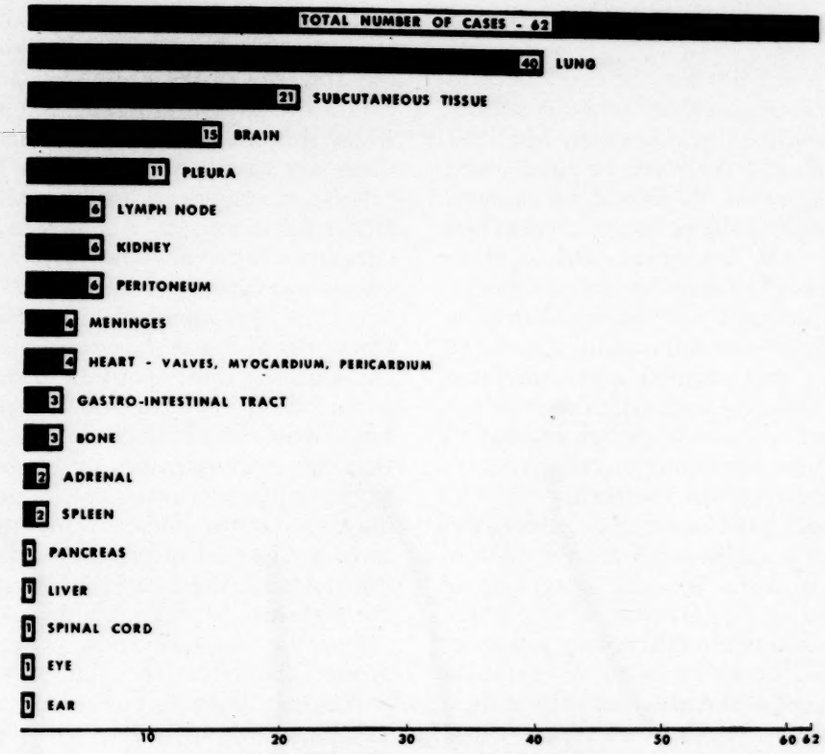

FIG. 3. Nocardiosis; organ involvement.

Clinical and Laboratory Diagnosis. While difficulties in obtaining suitable material for study are inherent in this disease, the diagnosis of nocardiosis might be established earlier and more frequently if the index of clinical suspicion were higher. The similarity between tuberculosis and fungus infections has been stressed by various authors,[23,24] and it has been urged that "nocardiosis should be considered in all patients with obscure or unusual chronic infections, especially when repeated attempts to demonstrate the tubercle bacillus have failed."[8] Perhaps we would stimulate more conclusive laboratory studies if we would separate in our own clinical thinking, not only tuberculosis and fungus infections but also actinomycosis and nocardiosis from other fungus infections, and if we were

aware of some of the common laboratory omissions and errors that occur frequently in this particular problem. Material is often sent to a laboratory with a notation of "questionable diagnosis of tuberculosis or fungus infection." Studies directed only toward tuberculosis and the more common fungus infections may lead to loss of valuable material or misinterpretation of laboratory results.

The acid-fast nocardias may be overlooked in routine acid-fast stains, as these acid-fast actinomyces vary in degree of acid-fastness. Modified acid-fast stains should therefore be used when nocardiosis is suspected. It should be remembered also that some of the pathogenic nocardias are not acid-fast (N. madurae), and in these infections even modified acid-fast stains will give no clue to the true nature of the organisms. In sputum the acid-fast nocardias readily undergo fragmentation so that isolated organisms may be mistaken for tubercle bacilli. Diligent search for variability in acid-fastness, in size and length of filaments, and for branching mycelia is therefore essential, as are culture methods.

Various authors have noted that concentration of sputum or pus with antiformin or sodium hydroxide, as is done for the diagnosis of tuberculosis will kill nocardia.[18,20,25] There appear to be certain strain differences, however, as others[11,21] did obtain growth of nocardia following treatment of the material with sodium hydroxide. It seems advisable therefore to avoid concentration methods whenever possible.

The bacteria-like and filamentous forms of nocardia are not easily recognized and are difficult to differentiate from artifacts in moist preparations, which are therefore of less value than in other fungus diseases such as blastomycosis or coccidioidomycosis.

Fragmentation of mycelia is frequent, particularly in the pathogenic species of nocardia and the organisms may resemble somewhat pleomorphic bacteria, such as diphtheroids. Shaw et al.[23] have noted that, especially on anaerobic incubation, diphtheroid configuration is common. Diphtheroids were isolated from an axillary abscess during life in one of Bernstein's patients,[21] who died shortly thereafter of widespread nocardiosis. Anaerobic diphtheroids were reported in one culture from the patient discussed in this paper. Unfortunately this culture was not available to us and one can therefore only speculate as to the true nature of the organisms. However, after the patient's death we were able to secure from laboratory A the tube of thioglycollate broth which had been inoculated with part of the same material which contained "unidentifiable filamentous material." There was minimal growth in the upper 2 mm. of the tube, the remainder of the broth being clear. Subculture of this growth revealed a pure culture of Nocardia asteroides, identical in all respects with the organism isolated by us from the abscesses of the chest wall and brain. This recalls the patient of Kirby and McNaught[19] in whose sputum gram-positive, slender, branching filaments were seen repeatedly but were considered insignificant until months later when Nocardia asteroides was isolated from a subcutaneous abscess. The aerobic actinomyces which was found repeatedly in the sputum and bronchial secretions of a patient reported by Connar et al.[14] was considered a non-pathogenic contaminant until about one month later when a pure culture of Nocardia asteroides was isolated from empyema pus. Smith[26] has stated that the demonstration of Nocardia asteroides in the sputum or other discharges establishes a diagnosis, but organisms of the nocardia species have been noted in the sputum of patients who did not have demonstrable clinical disease.[20,27] Nevertheless, in patients with an obscure clinical illness the demonstration of nocardia should arouse suspicion that the organism may be pathogenic. Also, in patients presenting a clinical picture compatible with nocardiosis the finding of diphtheroids should lead to further study. These organisms should not be discounted but should be preserved for further study and if necessary submitted to an experienced mycologist.

Nocardia grows well on most ordinary culture media such as infusion agar, agar enriched with blood or ascitic fluid, Czapek's medium or Sabouraud's medium. The strain of nocardia isolated from the patient reported here grew well on Sabouraud's medium but the growth was slower and less luxuriant than on blood or ascitic fluid agar. A specimen containing only few organisms might therefore have given negative results if Sabouraud's medium alone had been employed. We would recommend the use of enriched media and incubation under aerobic and anaerobic conditions for the diagnosis of fungus as well as bacterial disease, particularly if the clinical impression suggests the possibility of actinomycosis or nocardiosis.

With few exceptions pathogenic fungi are re-

TABLE II

SENSITIVITIES OF TWENTY-SIX STRAINS OF NOCARDIA

	Sulfadiazine	Penicillin	Streptomycin	Aureomycin	Chloramphenicol	Terramycin	Neomycin	PASA	Myvizone	N¹N-bis (thiocarbamyl) hydrazine	Diasone	Bacillomycin	Actidione	Promine	Polymyxin	Bacitracin	Pregnenolone acetate 1%	Penicillin and Streptomycin	Penicillin + Chloramphenicol	Penicillin + Terramycin + Chloramphenicol
																		Pen. SM	P C	P T C
Glover et al.[24]	12.5	>100	5																	
Hager et al.[20]	6.2	0.004	0.03																	
	>600	0.015	0.12	0.5																
Eckhardt and Pilcher[12]		>5	>40																	
Runyon[10]	4	500	4	4	25	16		5,000												
	4	500	4	4	25	16		5,000												
	4	500	4	4	25	16		5,000												
Mogabgab and Floyd[27]	10,000	10	60	25	50	25														
Strauss et al.[21]	>50	>200		10	20			200	10	20										
	>200			10	100	100			200	50										
	200			10	20	50			<1	50	>50									
	200		100	10	20	100		200		50										
			100	10	20	100				20	>200									
	50		100	<1	20	100	>50	100	10	10		>100	>20	>20						
				10	20	100		200	<1	10	>200									
				10	20	20		200	>200	10	100		>100							
	200	200		50	20	100			200	50	>100			>50						
			200	10	20	100		200	50	50				>50						
	50		200	50	100	100				10										
			50	<1	50	10	100		50											
		2	10	<1	10	<1	50			200										
		200	20	<1	10	20				200										
Cruz and Clancy[2]		R	R	R	R	1	Sl.								R					
Bernstein et al.[21]	R			R	R	R										R		22 + 40		
Wichelhausen et al.	5	>50	100	25	>100	>100													50 + 200	12.5 + 50 + 50
Lamb et al.[17]	>200	R	R	R	R	R										R	Partial Inhibition			

R = Resistant

(Details not reported)

Sl. = Slightly sensitive

sistant to antibiotics. Therefore it has become customary to attempt cultivation of pathogenic fungi from patients even while on antibiotic therapy. A different approach should be followed if actinomycosis or nocardiosis is suspected. Many strains of A. bovis are sensitive to penicillin, streptomycin or terramycin.[28,29] The sensitivity of various strains of nocardia to antibiotics differs widely.

Although Nocardia asteroides has been isolated from patients while they were receiving antibiotics,[24] it is possible that in an occasional case antibiotic therapy, though clinically ineffective, may interfere with the detection of the causative organism. Little is known about the synergistic effect of various antibiotics on nocardias. The strain isolated from our patient was not inhibited by 50 units of penicillin, 100 μg. of chloramphenicol or 100 μg. of terramycin. *In vitro* inhibition was achieved, however, when these three antibiotics were combined. (Table II.) It is of interest, though certainly not conclusive, that our patient had consistently negative cultures while on antibiotic therapy. He was not receiving any antibiotics at the time when positive cultures were finally obtained. (Table I.)

The finding of nocardia in blood culture has been reported only once.[19] Blood cultures should however be made, particularly if the question arises whether an organism isolated from another source is pathogenic or an insignificant contaminant.

Therapy. Most of the patients with nocardiosis who have recovered during the past eight years have received sulfadiazine, usually in combination with penicillin, streptomycin and/or surgical procedures. Recently improvement and recovery has been reported with aureomycin therapy[13] and following treatment with penicillin and streptomycin.[21] Of interest also is the observation of Lamb et al.[17] that pregnenolone favorably influenced the course of a patient with mycetoma due to an atypical strain of Nocardia asteroides. The work of Runyon[30] and Strauss et al.[31] has demonstrated the superiority of sulfadiazine in *in vivo* experiments, although other drugs such as streptomycin or aureomycin showed similar or greater effectiveness *in vitro*. This would suggest that antibiotics effective *in vitro* should be added to, rather than substituted for, the sulfonamides. The fact that several cases terminated fatally in spite of sulfadiazine treatment cannot be interpreted as failure of the drug, since most of these patients received such therapy late in the disease and for periods of less than two weeks. From the information available it appears advisable to treat all patients with one of the sulfonamides as soon as the diagnosis of nocardiosis has been established, and to add other antibiotics as indicated by sensitivity studies or clinical course.

Medical therapy does not obviate the need for surgical measures in many cases of nocardiosis. Next to actinomycosis due to Actinomyces bovis, nocardiosis is perhaps the fungus disease of greatest interest to the general surgeon, thoracic surgeon and neurosurgeon. The frequency of brain abscesses, usually first seen by the neurologist or neurosurgeon, has already been emphasized. The general surgeon who is called upon to institute drainage of subcutaneous abscesses is in a good position to suspect the disease in its beginning, as these abscesses are characteristically deep-seated, may penetrate fascia and muscle and do not respond to the usual surgical and antibiotic measures. Surgical drainage may be an important part of treatment of pulmonic abscesses and empyema which fail to resolve under medical treatment.

SUMMARY

1. The case of a thirty-five year old white man, who was undiagnosed for sixteen months and subsequently found to have nocardiosis, is reported. The diagnosis was established only one week prior to death.

2. The clinical findings of nocardiosis are discussed.

3. The literature is reviewed with particular emphasis on diagnostic procedures and on interpretation of laboratory results.

4. It is urged that nocardiosis be considered as a diagnostic possibility in patients with pulmonary and brain involvement or in cases with multiple abscesses of undetermined etiology.

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Venous "Spiders" in Chronic Lymphatic Leukemia*

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THIS report describes venous vascular formations of the skin in a patient with chronic lymphatic leukemia. Although these lesions resembled the arterial spider usually associated with chronic liver disease, they proved to be venous in origin and were thought to be associated with the patient's leukemia rather than a result of liver involvement.

A number of vascular formations of the skin have been described in association with various diseases and in normal persons. It is difficult to classify these lesions. Ormsby and Montgomery[7] use the following classification: (1) angiomas, characterized by new growth of vessels and (2) telangiectases, a dilatation of pre-existing vessels without new vessel formation. A combination of the two types may occur. Spider-like lesions are usually classified as acquired telangiectases. At times, however, they may show development of new vessels.[4,7]

There are three possible forms of vascular spiders: (1) arterial forms with either an overgrown end-artery in the skin, or a coiled, thickened artery in the subcutis, both with branching arterioles and capillaries;[1,5] (2) direct arteriovenous anastomoses with radiating tributaries;[4,8] and (3) tiny veins or capillaries terminating in a central vein, as characterized by the venous star described by Bean.[1]

The arterial spider, or nevus araneus, has been studied extensively by Bean and others.[1–3] It consists of a central, elevated and erythematous body about 1 mm. in diameter and represents a dilated end-artery. From this body radiate dilated, vascular branches giving the appearance of a spider. Pulsation of the center of these lesions can usually be demonstrated by touch or by pressure over the area with a glass slide. Blood flow is centrifugal. The entire lesion may be 2 cm. in size and is usually located on the face, neck, thorax or upper extremities in varying numbers. It has been seen in association with uncomplicated pregnancy and in normal persons, as well as in chronic liver disease, thyrotoxicosis, xeroderma pigmentosum, chronic x-ray dermatitis, lupus erythematosus, Raynaud's disease, Cushing's disease, and rheumatic fever (probably due to associated cardiac cirrhosis).[2,7] Among the liver diseases in which it occurs, the following have been reported: Laennec's cirrhosis, hepatitis, cardiac cirrhosis, common duct stone with obstruction, primary hepatoma, liver metastases, hemochromatosis, toxic hepatitis due to arsenicals or bismuth, fatty liver and Weil's disease.[3]

The venous star, which may resemble the arterial spider, has been described by Bean[1] as follows: it is a blue or red circumscribed area in the skin caused by dilated, underlying veins, the result of venous obstruction with persistent elevation of venous pressure. It has been seen particularly in superior vena caval obstruction. This lesion is usually found overlying veins of large size into which it empties. Although the blood flow is toward the center, the vessels will fill by reflux from the center after pressure. The venous star is seen commonly along the lower borders of the ribs, on the dorsum of the foot, around the ankles and lower portion of the legs and on the medial aspect of the thighs. It also may be seen on the back at the junction of the neck and thorax, or just above the sacrum. These lesions may occur in children but are more common after adolescence and in women.

CASE REPORT

F. R., a thirty-seven year old, white electrician, had a diagnosis of chronic lymphatic leukemia made in 1951 by blood studies and

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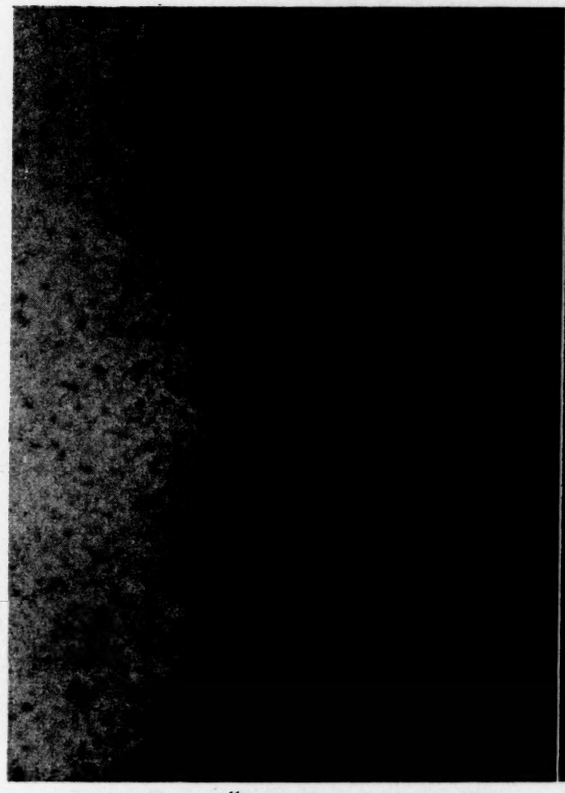

FIG. 1. Venous "spider" on right shoulder.

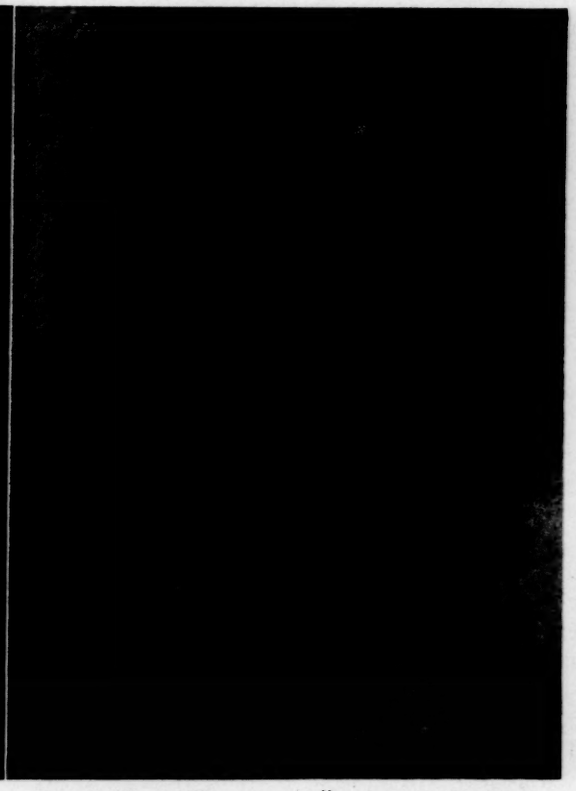

FIG. 2. Nipple-like center of "spider" on shoulder.

lymph node biopsy. His disease was characterized by generalized lymphadenopathy, lymphocytosis of mature type, a liver palpated two to three fingerbreadths below the right costal margin, and questionable splenomegaly. Liver function studies on two different occasions showed a maximal BSP dye retention of 12 per cent in one-half hour with 5 mg. of dye per kg. of body weight, a cephalin flocculation test of 3 plus, a thymol turbidity of 1 unit, normal prothrombin time and normal serum bilirubin.

The skin lesions, first noticed on his admission to the hospital two years previously, appeared as diffuse, erythematous areas approximately 1 cm. in diameter with a rich, vascular bed arranged in radial fashion about a 1 to 2 mm., elevated, nipple-like, reddish-yellow center. Figures 1 and 2 show the spider-like lesion on the shoulder. The nipple-like center is well demonstrated with side lighting. There were several of these lesions scattered about the upper thorax and shoulders. No arterial pulsation could be demonstrated; the direction of blood flow could not be determined. During the two years of observation some of the spiders disappeared, others were noted to become smaller.

Biopsy of one of these areas showed the nipple-like center to be due to slight hyperkeratosis of the epithelium overlying an irregular, dilated venule containing fibrin. Surrounding this central venule were a few smaller venules and occasional arterioles. The arterioles were partially obliterated by fibrin clots and organization was present in one. In the surrounding connective tissue there was a light infiltrate of lymphocytes. Figure 3 shows a cross section through one of the lesions, demonstrating the papular center with thrombosed central vein and surrounding smaller blood vessels beneath. The pathologic diagnosis was fibrin thrombi in dilated, superficial blood vessels of the skin.

COMMENTS

Localized or generalized cutaneous lesions which occur in leukemia may appear as nodular, macular, papular, erythematous or hemorrhagic areas and are due to infiltration of the skin by the leukemic cells.[4,7] Venous thrombi in association with metastatic leukemic infiltrations have been reported but in none of these cases did the lesions resemble a "spider." Madden[6] described tel-

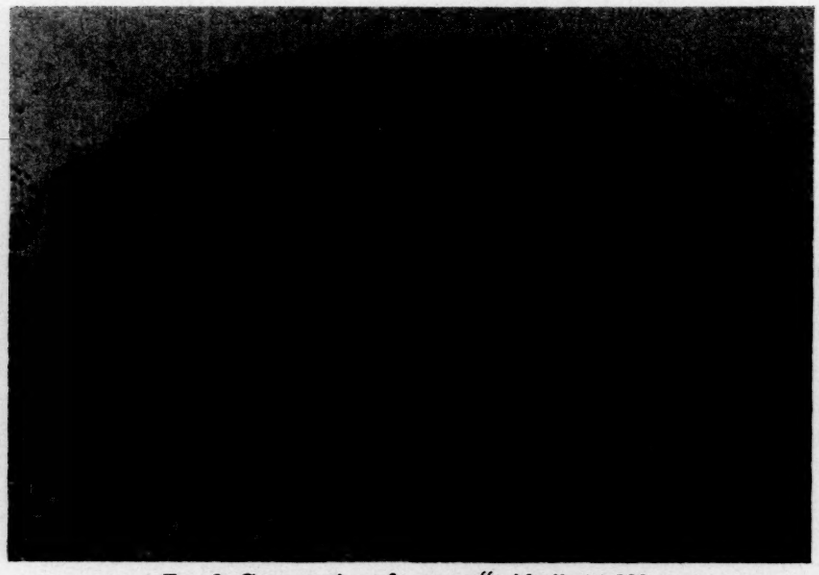

FIG. 3. Cross section of venous "spider"; × 220.

angiectatic areas in association with myelogenous leukemia and others have described telangiectasis in leukemia but in none of these cases did the lesions resemble "spiders."

In the case presented it appeared that the vascular formations were related to thrombosis of veins. The immediate cause of this thrombosis was not evident but may well have been related to the primary disease process. Sufficient leukemic cell infiltration in the center of these lesions was not present to suggest a direct, causal relationship on that basis.

SUMMARY

Several types of vascular "spiders" of the skin are described. The occurrence of several spider-like lesions of venous origin in a patient with chronic lymphatic leukemia during a two-year period of observation is reported. The venous spiders in this patient were at first mistaken for the arterial spider associated with chronic liver disease.

Acknowledgment: Photographs were made by the Medical Illustration Laboratory, Veterans Administration Hospital, Atlanta, Georgia.

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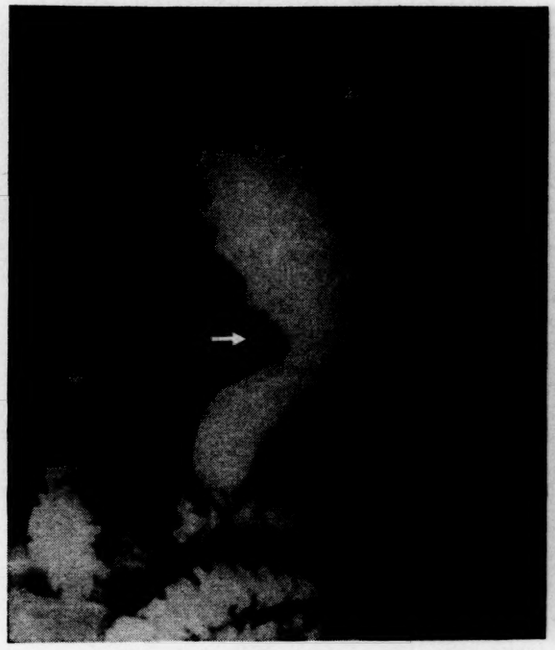

Fig. 1 "Roentgen examination . . . revealed the ulcer to be very much in evidence."

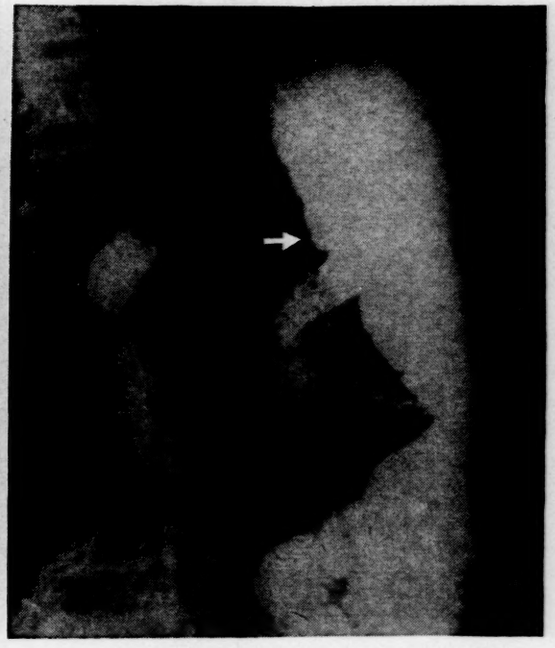

Fig. 2 In ten weeks "the ulcer niche was no longer in evidence roentgenologically or gastroscopically."

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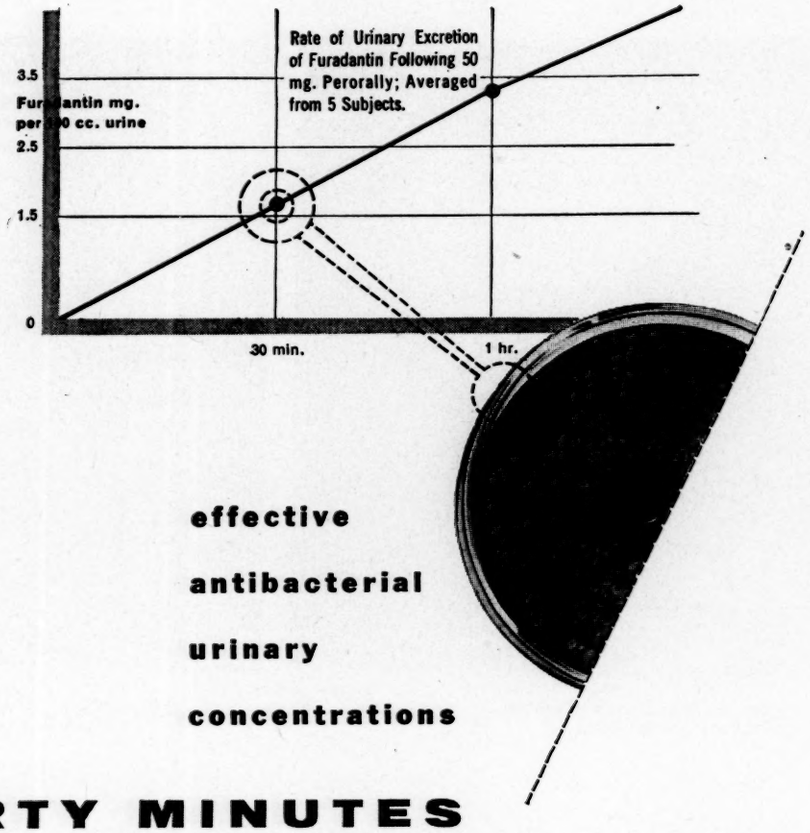

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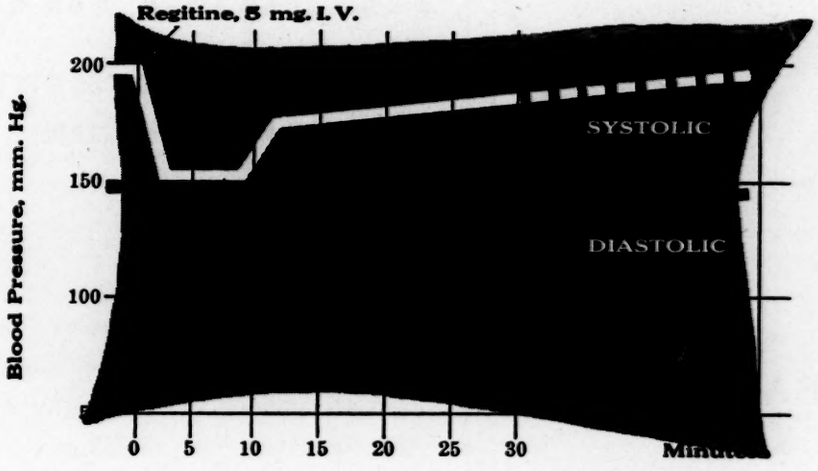

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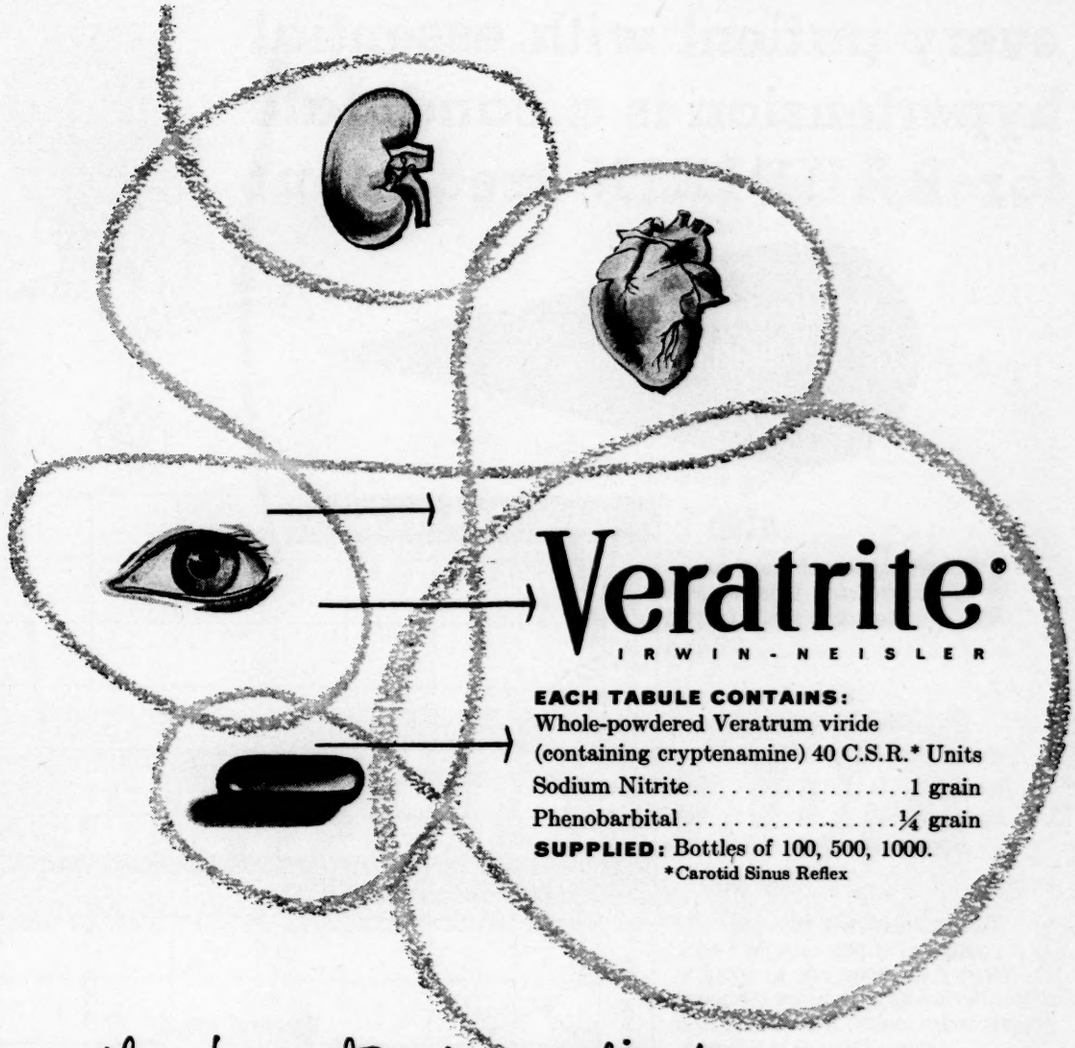

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Sodium Nitrite . . . . . 1 grain
Phenobarbital . . . . . ¼ grain
SUPPLIED: Bottles of 100, 500, 1000.
*Carotid Sinus Reflex

for the hypertensive patient

A DRUG OF SEASONED JUDGEMENT

Fifteen years of research, clinical studies and practical experience in many thousands of ambulatory patients have established an unequaled record of efficacy combined with safety for the Veratrum viride preparations of Irwin-Neisler.

Veratrite tabules provide the best effects of Veratrum viride in a form especially suited to the long-term management of the large majority of hypertensive patients.

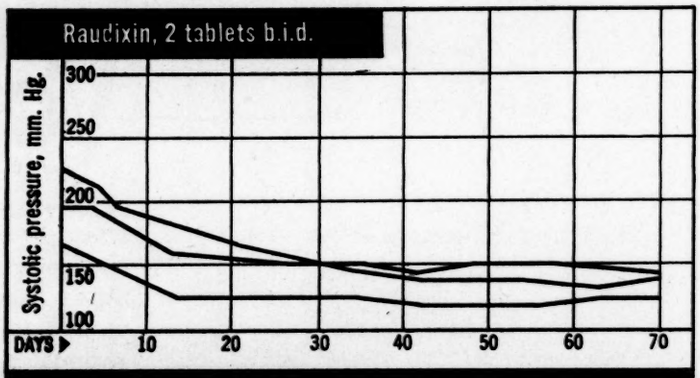
IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

every patient with essential hypertension is a candidate for RAUDIXIN treatment

Because of its safety, RAUDIXIN is the drug to use first:

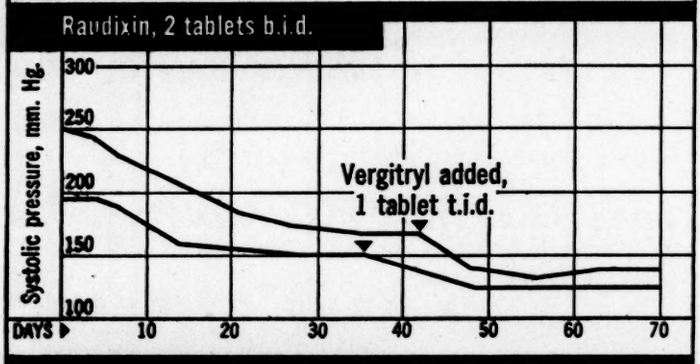
step 1

Raudixin controls most cases of mild to moderate hypertension, and some severe cases.



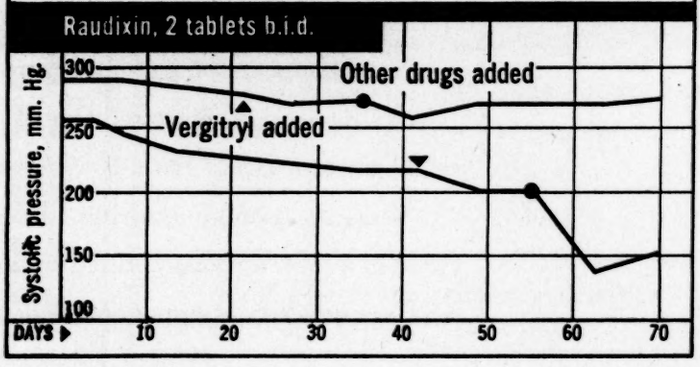
step 2

If blood pressure is not adequately controlled in four to eight weeks, Vergitryl (veratrum) may be added to Raudixin. This brings many of the remaining patients under control. Raudixin tends to delay tolerance to Veratrum, and makes smaller dosage possible.



step 3

For the few patients resistant to this combined regimen, a more potent drug may be added, for example, Bistrium (hexamethonium). The most potent drugs, which are potentially dangerous, are thus used only as a last resort in the most refractory cases.



RAUDIXIN
Squibb rauwolfia

50 mg. tablets containing the whole powdered root of Rauwolfia serpentina
Bottles of 100 and 1000

"RAUDIXIN" "VERGITRYL"® AND "BISTRIUM"® ARE TRADEMARKS

SQUIBB manufacturing chemists to the medical profession since 1858

IN THE COMMON COLD...

Prompt Symptomatic Relief with

Multihist* + APC

MULTIPLE ANTIHISTAMINE •
ANALGESIC • ANTIPYRETIC

Taken at the onset of symptoms, Multihist + APC quickly suppresses the troublesome rhinorrhea of the common cold and relieves such general symptoms as headache, backache, and other discomfort. Each capsule provides 15 mg. of the Multihist combination (5 mg. each of Pyrilamine maleate, Prophenpyridamine maleate, and Phenyltoloxamine dihydrogen citrate) together with aspirin 3½ gr., phenacetin 2½ gr., and caffeine ½ gr. Because each antihistamine is provided in an amount virtually incapable of producing drowsiness or lethargy, the incidence of side effects is greatly reduced. Average dose, 2 capsules initially, followed by 1 capsule at 4-hour intervals. Available on prescription through all pharmacies.

SMITH-DORSEY
Lincoln, Nebraska
A Division of THE WANDER COMPANY

* **multiple antihistamine therapy means reduced incidence of side effects**

IN URINARY TRACT INFECTIONS
SULFOSE EXCELS

In Every Medical Dimension

Higher and more prolonged blood levels than with other sulfonamide preparations, single or in combination.

Superior tissue distribution, owing to higher sulfonamide blood levels. Cecil says, ". . . infection is in tissues and not in the lumen of the urinary passages."

Antibacterial action—particularly effective against E. coli.

Greater solubility in acid urine—With pH below 6 —common in infection— Sulfose and its acetylated fractions give greater solubility than the single sulfonamides—sulfisoxazole and sulfadimetine.

References available

SULFOSE®

TRIPLE SULFONAMIDES WYETH

SUSPENSION TABLETS

Wyeth®
PHILADELPHIA 2, PA.

NEW... council-accepted oral anticoagulant *(not a coumarin derivative)* with a wide range of safety

HEDULIN®

(Brand of Phenindione, 2-phenyl-1,3-indandione)

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

Permits dependable prothrombin control with little risk of dangerous fluctuations

- **HEDULIN is not cumulative in effect—provides greater uniformity of action and ease of maintenance**
- **HEDULIN is rapidly excreted—therapeutic effect dissipated within 24-48 hours if withdrawal becomes necessary**
- **HEDULIN acts promptly, producing therapeutic prothrombin levels in 18-24 hours**
- **HEDULIN requires fewer prothrombin determinations—only one in 7 to 14 days, after maintenance dose is established**
- **HEDULIN's anticoagulant action is rapidly reversed by vitamin K_1 emulsion**

DOSAGE: 4 to 6 tablets (200 to 300 mg.) initially, half in the morning and half at night; maintenance dosage (on basis of prothrombin determinations daily for first three days), 50 to 100 mg. daily, divided as above.

Available on prescription through all pharmacies, in original bottles of 100 and 1000 50-mg. scored tablets.

Complete literature to physicians on request

Walker LABORATORIES, INC., MOUNT VERNON, N. Y.

*Registered trademark of Walker Laboratories, Inc.

improve
capillary
resistance
in prevention
and treatment of
capillary fragility
capillary hemorrhage
vascular accidents

C.V.P.

(CITRUS FLAVONOID
COMPOUND
WITH VITAMIN C)

Five years of laboratory and clinical investigations establish the complete safety and value of C.V.P. in increasing capillary resistance and reducing abnormal bleeding due to capillary fragility.

C.V.P. provides natural bio-flavonoids (whole natural vitamin P complex) derived from citrus sources—potentiated by vitamin C—which act synergistically to thicken the intercellular ground substance (cement) of capillary walls, decrease permeability . . . and thus increase capillary resistance.

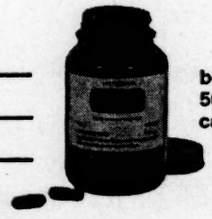
may protect against abnormal bleeding and vascular accidents in . . .

- **hypertension**
- **retinal hemorrhage**
- **diabetes**
- **radiation injury**
- **purpura**
- **tuberculous bleeding**

"Many instances of hemorrhage and thrombosis in the heart and brain may be avoided if adequate amounts of vitamin P and C are provided."

each C.V.P. capsule provides:	
Citrus Flavonoid Compound*	100 mg.
Ascorbic Acid (C)	100 mg.

*(water soluble whole natural vitamin "P" complex, more active than insoluble rutin or hesperidin)



bottles of 100,
500 and 1000
capsules

Professional samples and literature on request.

USV **u. s. vitamin corporation**
Casimir Funk Laboratories, Inc. (affiliate)
250 East 43rd Street, New York 17, N.Y.

A new form of a synthetic narcotic analgesic . . . approximately twice as potent as racemic Dromoran (dl) Hydrobromide 'Roche' . . . inducing prompt pain relief with longer duration of analgesic effect than morphine.

. . . indicated for the relief of severe or intractable pain . . . preoperative medication and postoperative analgesia.

. . . "A striking characteristic is its ability to produce cheerfulness in pain-depressed patients the morning after an evening dose."*

. . . less likely than morphine to produce constipation, nausea or other undesirable side effects . . . whether administered orally or subcutaneously.

LEVO-DROMORAN

TARTRATE *'Roche'*

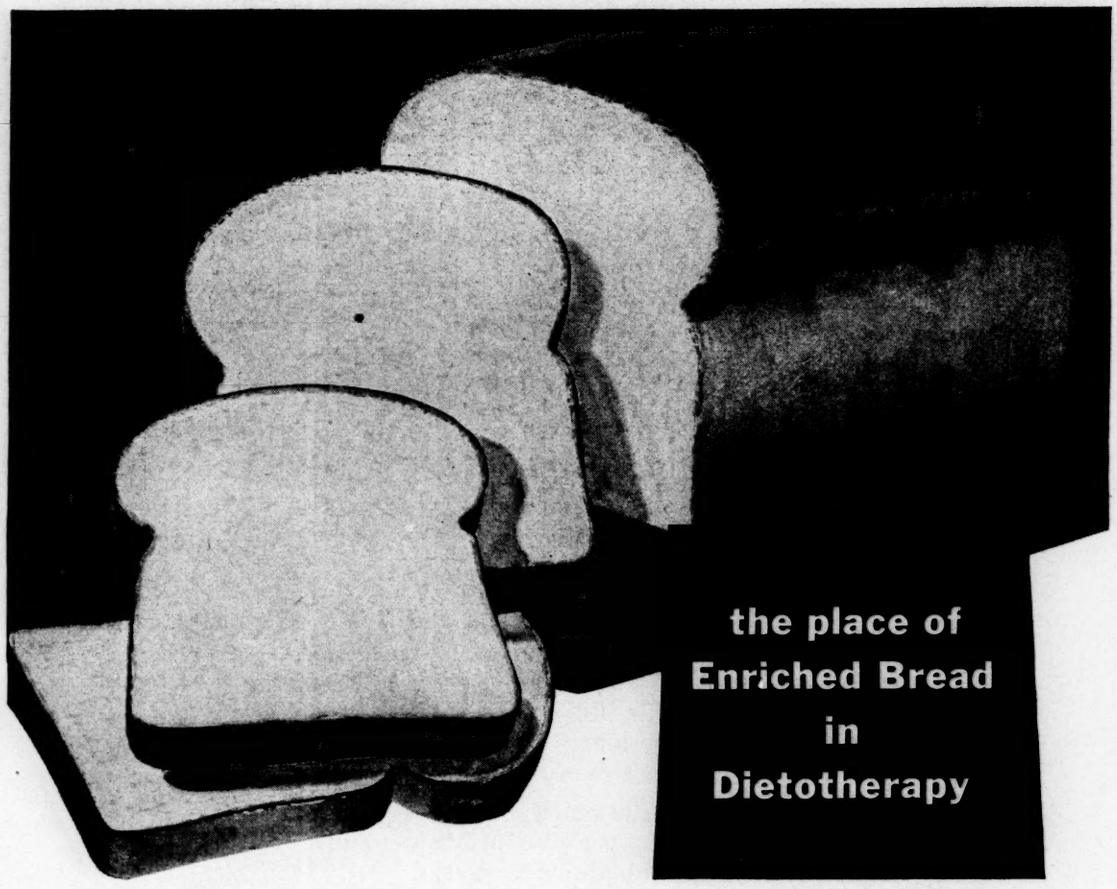
(tartaric acid salt of levo-3-hydroxy-N-methylmorphinan)

CAUTION:
Levo-Dromoran Tartrate is a narcotic analgesic. It has an addiction liability equal to morphine and therefore the same precautions should be taken in dispensing this drug as with morphine.

*Glazebrook, A. J.: Brit. M. J., 2:1328 (Dec. 20) 1952.

HOFFMANN-LA ROCHE INC • Nutley 10 • New Jersey

LEVO-DROMORAN®—brand of levorphan



In the many instances encountered in everyday practice when dietary adjustment assumes a therapeutic role, the special diet gains in nutritional value when the bread included is enriched bread.

Enriched bread, today the bulk of commercial bread, contains important amounts of added B vitamins, iron, and in most instances nonfat milk solids. Because it supplies significant quantities of essential nutrients that are metabolically required regardless of the condition under treatment, enriched bread deserves a place in virtually all special purpose diets, including those for weight reduction. In the latter, two or three slices of enriched bread, the quantity usually allowed, contribute needed calories as well as essential nutrients in noteworthy amounts.

In compliance with government regulations, enriched bread, per pound, provides at least 1.1 mg. of thiamine, 0.7 mg. of riboflavin, 10 mg. of niacin, and 8 mg. of iron. By and large, enriched bread as marketed also supplies about 400 mg. of calcium and 39 Gm. of protein. Since the protein consists of flour and milk proteins, it is biologically valuable for growth as well as tissue maintenance. Thus enriched bread can make a significant contribution to the satisfaction of daily requirements in dietotherapy.

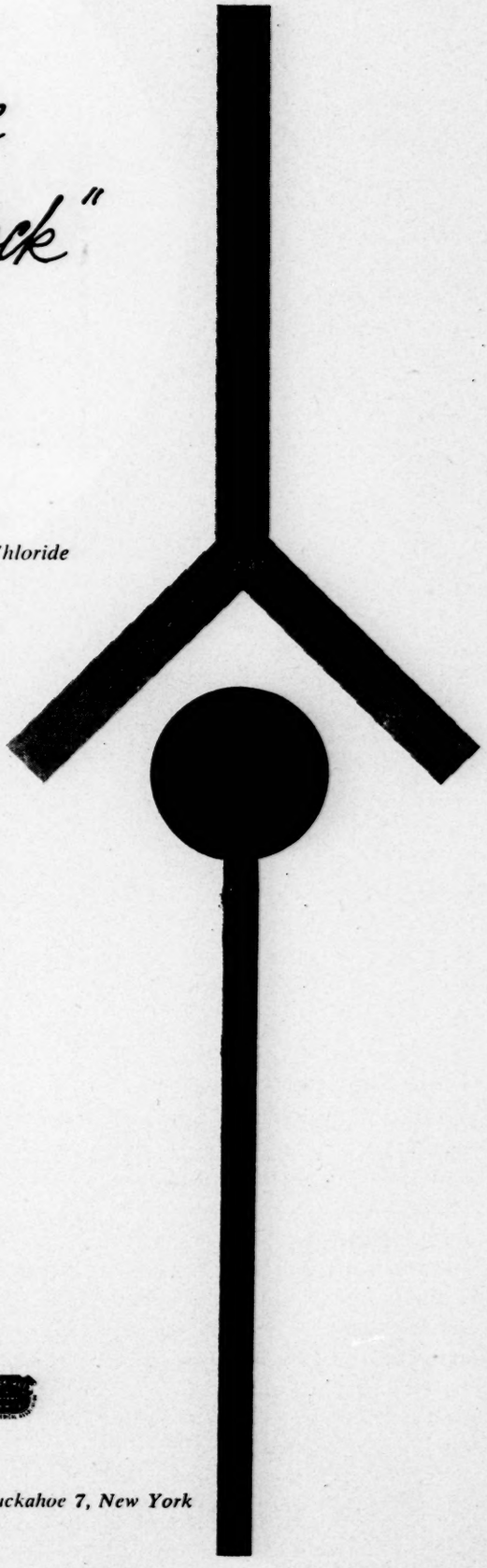
Bread rounds out virtually every diet. Because it is readily digested and contains only an insignificant amount of indigestible residue, enriched bread is rarely—if ever—contraindicated.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

AMERICAN BAKERS ASSOCIATION

20 North Wacker Drive • Chicago 6, Illinois

Ganglionic "road-block" in hypertension



'HEXAMETON'® *Chloride*

. . . a well-proven *powerful* hypotensive agent—for use in certain types of hypertension and peripheral vascular disease

. . . patients must be properly selected and dosage closely controlled—particularly initially

. . . detailed information available on indications, dosage, and precautions.

FOR INJECTION

'HEXAMETON' *Chloride brand Hexamethonium Chloride Injection*

Each cc. contains 25 mg. or 100 mg. Hexamethonium ion

Each strength in multiple-dose vials of 10 cc.

FOR ORAL USE

'HEXAMETON' *Chloride brand Hexamethonium Chloride Compressed 250 mg. and 500 mg.*

Both strengths scored

Each strength in bottles of 100 and 1,000

BURROUGHS WELLCOME & CO. (U.S.A.) INC. *Tuckahoe 7, New York*

In infections and allergic rhinitis and sinusitis

Biomydrin "is effective as an antibiotic in clearing the nose of pathogenic organisms and purulent secretions. In many cases, sterile cultures were obtained after a brief period of treatment."

Antibiotics & Chemotherapy *3*:299 (March) 1953.

Improvement in 113 of 124 Patients*

Diagnosis	Number of patients	Improved
Chronic catarrhal rhinitis	11	11
Chronic allergic rhinitis	26	25
Right maxillary sinusitis	2	1
Chronic naso-pharyngeal catarrh	6	6
Chronic suppurative sinusitis	3	3
Coryza, Head cold, Catarrhal rhinitis	58	51
Influenza	2	1
Acute catarrh	4	3
Hypertrophic rhinitis	12	12
TOTAL	124	113 (91.1%)

* Eye, Ear, Nose and Throat Monthly *32*:512 (Sept.) 1953.

The Biomydrin formula

THONZONIUM BROMIDE 0.05%. Synthesized in the Nepera laboratories. Exceedingly potent antibacterial. Greatly enhances the antibiotic activity of neomycin and gramicidin. Reduces surface tension, facilitating spreading and penetrating. Mucolytic.

NEOMYCIN SULFATE 0.1%. Effective against gram-positive and gram-negative organisms.

GRAMICIDIN 0.005%. Effective against gram-positive organisms.

PHENYLEPHRINE HCl 0.25%. Widely preferred vasoconstrictor.

THONZYLAMINE HCl 1.0%. *Therapeutic concentration* of this effective antihistaminic aids in controlling local allergic manifestations.

- Prompt, prolonged shrinkage of nasal mucosa without secondary congestion.
- pH is 6.2. Isotonic and buffered.
- Does not interfere with ciliary activity.
- Spray covers larger area than could be reached by drops.
- Available on prescription only.

DOSAGE: Adults—2 or 3 sprays in each nostril; 4 or 5 times a day as needed, or as directed by physician. Children—1 or 2 sprays in each nostril; 4 or 5 times a day as needed, or as directed by physician.

BIOMYDRIN

Nepera Chemical Co., Inc. Pharmaceutical Manufacturers, Yonkers 2, N. Y.

Meat...

and Its Place in the Diet in Hypertension

Contrary to the concept that protein intake contributes to the genesis of hypertension and should be drastically reduced in therapy[1, 2, 3] adequate protein nutrition today is considered essential for preserving maximal vigor and a sense of well-being in the hypertensive patient.[3] Meat, once thought to be contraindicated, now is recognized as an important protein food in the dietary regimen in hypertension.

High-protein foods do not elevate arterial tension — neither in the hypertensive nor the normotensive person. Nor does the specific dynamic action of protein make undue demands on the heart.[2, 3, 4] Only in advanced hypertension when renal function is seriously impaired, or in cardiac emergency episodes, when cardiac disease complicates hypertension, is restriction of protein intake below the normal allowance of 60 to 70 Gm. per day justifiable.[2, 3]

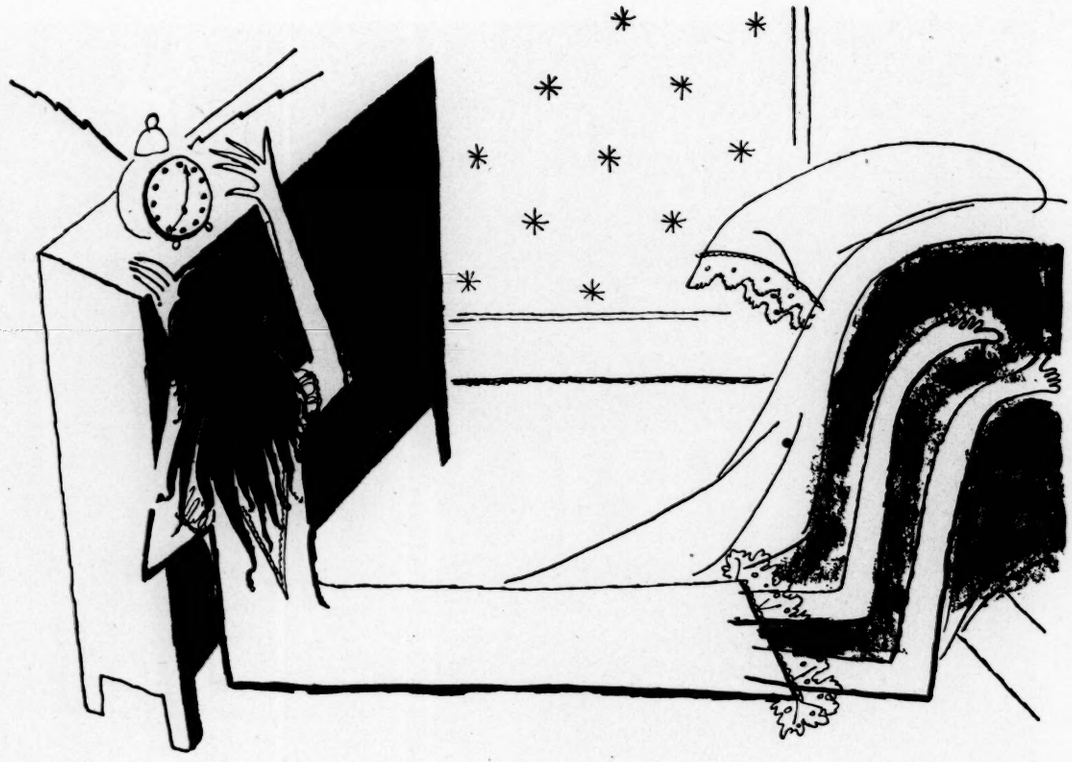
But not only for its high content of biologically top-quality protein is meat a recommended daily food in the diet of the hypertensive patient. It also goes far toward satisfying the needs for essential B vitamins and minerals. Another important feature of meat is its outstanding taste appeal and its virtually complete digestibility.

---

1. Wilhelmj, C. M.; McDonough, J., and McCarthy, H. H.: Nutrition and Blood Pressure, Am. J. Digest. Dis. *20*:117 (May) 1953.
2. Mann, G. V., and Stare, F. J.: Nutritional Needs in Illness and Disease, J.A.M.A. *142*:409 (Feb. 11) 1950.
3. McLester, J. S., and Darby, W. J.: Nutrition and Diets in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, 1952, pp. 519-524.
4. Levine, V. E.: The Blood Pressure of the Eskimo, Federation Proc. *1*:121 (Mar. 16) 1942.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute
Main Office, Chicago... Members Throughout the United States



Common Iron Deficiency Anemia?

THREE **IBEROL** TABLETS
the daily therapeutic dose, supply:

- Ferrous Sulfate..... 1.05 Gm.
  (representing 210 mg. elemental iron, the active ingredient for the increase of hemoglobin in the treatment of iron-deficiency anemia)

Plus these nutritional constituents:

- Thiamine Mononitrate..... 6 mg. (6 times MDR*)
- Riboflavin (3 times MDR*) 6 mg.
- Nicotinamide ..... 30 mg. (2 times RDA†)
- Ascorbic Acid ..... 150 mg. (5 times MDR*)
- Pyridoxine Hydrochloride.. 3 mg.
- Pantothenic Acid..... 6 mg.
- Vitamin B_{12}..... 30 mcg.
- Folic Acid..... 3.6 mg.
- Stomach-Liver Digest.... 1.5 Gm.

*MDR—Minimum Daily Requirement
†RDA—Recommended Daily Dietary Allowance

JUST one IBEROL tablet t.i.d. assures a therapeutic dose of iron, ascorbic acid, seven B complex factors including B_{12} and folic acid, and—to conserve the hematopoietic factors—standardized stomach-liver digest. The triple-coated, compressed tablets have an outer sugar coating to mask the iron in the middle coating. No unpleasant liver odor or taste.

In pregnancy, old age or convalescence, one or two tablets daily are usually enough. IBEROL may be used as a supplemental hematinic in pernicious anemia. Available in bottles of 100, 500 and 1000. Abbott

specify **IBEROL®**

(Iron, B_{12}, Folic Acid, Stomach-Liver Digest, with Other Vitamins, Abbott)

I-245

PHOTOGRAPH BY MILTON GREENE

Gouty arthritic gets back in the swing with...

BENEMID.

PROBENECID

BENEMID helps bring motion back to gouty arthritic joints—helps even your bedridden patients return to normal living.

BENEMID is considered a most effective and harmless uricosuric agent.[1] Without any restrictions in diet, serum uric acid levels return to normal range... resulting in "marked decrease in frequency and severity of acute attacks and diminution of intercritical symptoms."[2]

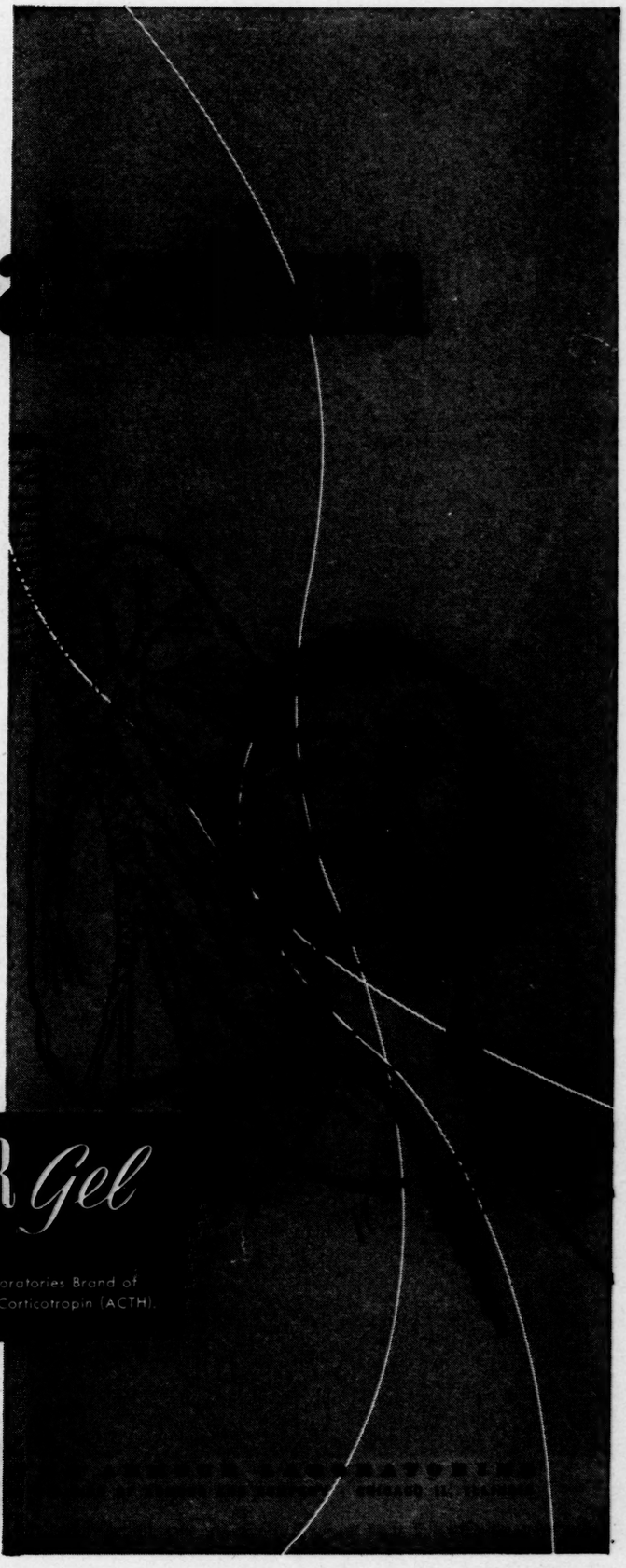
Current investigations indicate BENEMID also retards and prevents deposition of new tophi. Old tophi diminish and sometimes disappear altogether.[3]

Quick Information: BENEMID is available in *0.5 Gm.* tablets. *Dosage:* 1 to 4 tablets daily. *Contraindication:* Renal impairment.

References: 1. J.A.M.A. 149:1188, July 26, 1952. 2. Bull. Vancouver M.A. 29:306, 1953. 3. Current Med. Digest: 20:9, Sept. 1953.

FOR RAPID AND
SUSTAINED RELIEF IN

bronchia



HP*ACTHAR *Gel* meets the practical requirements for successful treatment of bronchial asthma in the patient's home and the physician's office. The need for hospitalization is greatly reduced, even in severe cases.

HP*ACTHAR *Gel* acts rapidly—essential in the acute paroxysms of asthma. Therapeutic action is sustained over prolonged periods of time, resulting in a diminished need for injections: One or two per week suffice in many instances.

HP*ACTHAR *Gel* can be a life-saving measure in status asthmaticus. Remissions up to 18 months duration have been reported.

HP*ACTHAR *Gel*

*Highly Purified

HP* ACTHAR* Gel is The Armour Laboratories Brand of Purified Adrenocorticotropic Hormone—Corticotropin (ACTH).

Subcutaneously
or intramuscularly as desired
with Minimum Discomfort
Home and Office Treatment
Greatly Simplified
Significant Economy

A


NOW an Improved Combination

ERYTHROCIN with SULFAS

TRADE MARK

Erythromycin Stearate with Triple Sulfas

Improved Blood Level Pattern — More rapid blood levels (usually within 2 hours). Consistent, significant levels for 8 hours.

Improved Absorption — Carefully-balanced buffer system protects ERYTHROCIN Stearate from gastric secretions. Assures swift absorption of drug in upper intestinal tract.

Improved Formulation — Each component is administered in the established dosage range of the drug. One appears to potentiate the other.

Improved Erythromycin Form — Marketed only by Abbott—ERYTHROCIN *Stearate*—eliminates the need of an enteric coating. Thus, permits more rapid absorption of drug.

Improved Dosage Form — Totally new and different type of *Film Sealed* tablet is conventionally sized. *Film Sealing* provides an almost invisible glaze that facilitates easy swallowing, completely masks taste of the drug. Abbott

each

ERYTHROCIN with SULFAS Tablet

represents:

ERYTHROCIN (as ERYTHROCIN stearate)	75 mg.
Sulfadiazine (as sodium salt)	111 mg.
Sulfamerazine (as sodium salt)	111 mg.
Sulfamethazine	111 mg.

With aluminum hydroxide as buffer

1-77-54

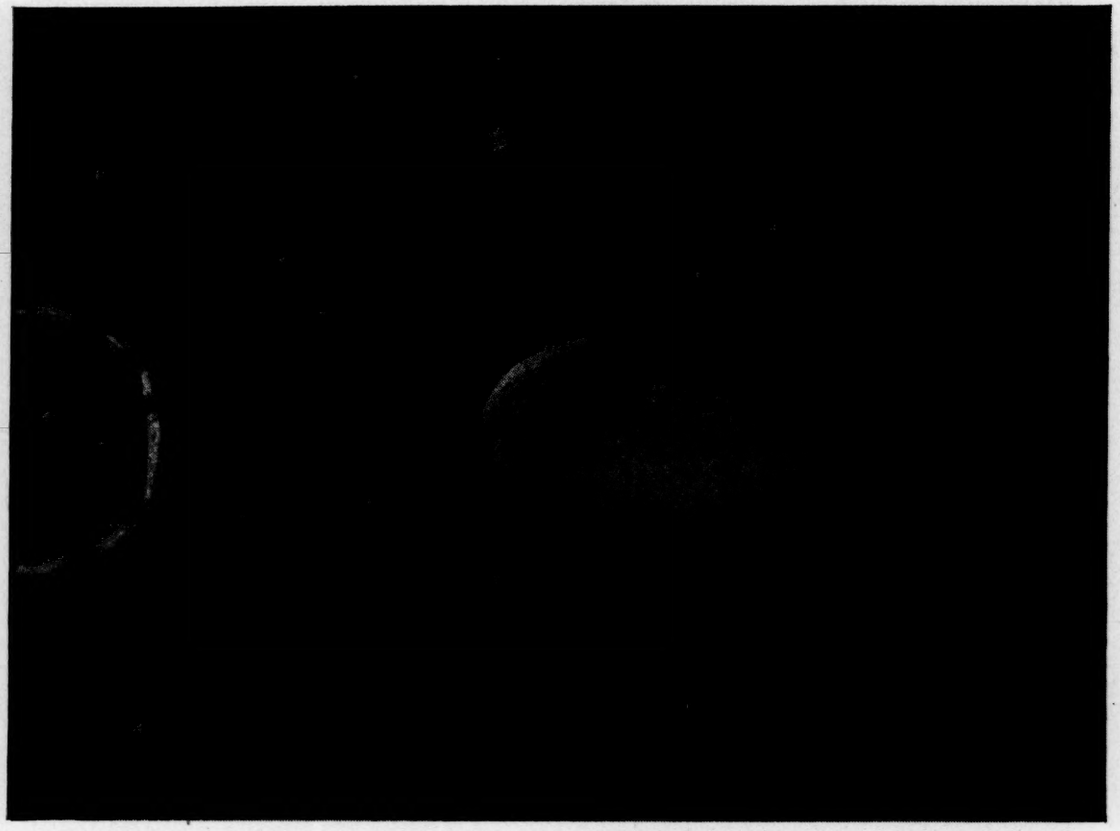
Chloromycetin®

(Chloramphenicol, Parke-Davis)

Since its introduction over four years ago, Chloromycetin has been used by physicians in practically every country of the world. More than 11,000,000 patients have been treated with this important antibiotic—

truly one of the world's outstanding therapeutic agents.

PARKE, DAVIS & COMPANY DETROIT 32, MICHIGAN



Retinal hemorrhage due to anticoagulant overdosage.

Dependable antidote for anticoagulant hemorrhage

EMULSION OF

MEPHYTON®

(EMULSION OF VITAMIN K_1, MERCK)

ACTION: MEPHYTON brings a new dimension of safety to anticoagulant therapy inducing hypoprothrombinemia. It is the *only* dependable agent for restoring normal prothrombin levels in anticoagulant-induced hypoprothrombinemia. Equally effective in various vitamin K deficiency states, MEPHYTON provides the most rapid, most complete, and most prolonged response yet attained.

OTHER INDICATIONS: Hypoprothrombinemia due to oral antibiotics and sulfonamides, salicylates, obstructive jaundice, hepatic disease, impaired gastrointestinal absorption, and hemorrhagic disease of the newborn; prophylactically prior to surgery, where hypoprothrombinemia is a possibility.

SUPPLIED: In boxes of six 1 cc. ampuls, each cc. containing 50 mg. of Vitamin K_1.

RELIEF

GED EFFECT

BRONCHIAL ASTHMA

SUS-PHRINE

AQUEOUS EPINEPHRINE SUSPENSION 1-200

Brewer

for subcutaneous injection

Increasingly favored as evidenced in—

RECENT CLINICAL REPORTS

. . . in 173 patients . . . all but three stated emphatically that they prefer the new product (Sus-Phrine) to epinephrine in oil . . . Greatest individual acceptances of the new injection has been by children.

Unger, A. H. and Unger, L. Annals of Allergy. 10:128,1952.

This free flowing aqueous suspension (Sus-Phrine) represents a distinct departure from previously available heavy, viscous preparations . . . it possesses marked advantages chiefly because of the small quantity required . . . and ease of administration. Since the material permits use of a short, small needle, it diminishes the psychological fear reaction which the sight of a long, large needle elicits in youngsters and in nervous apprehensive adults.

Jenkins, M. C. Jl. National Med. Assoc. 45:120,1953.

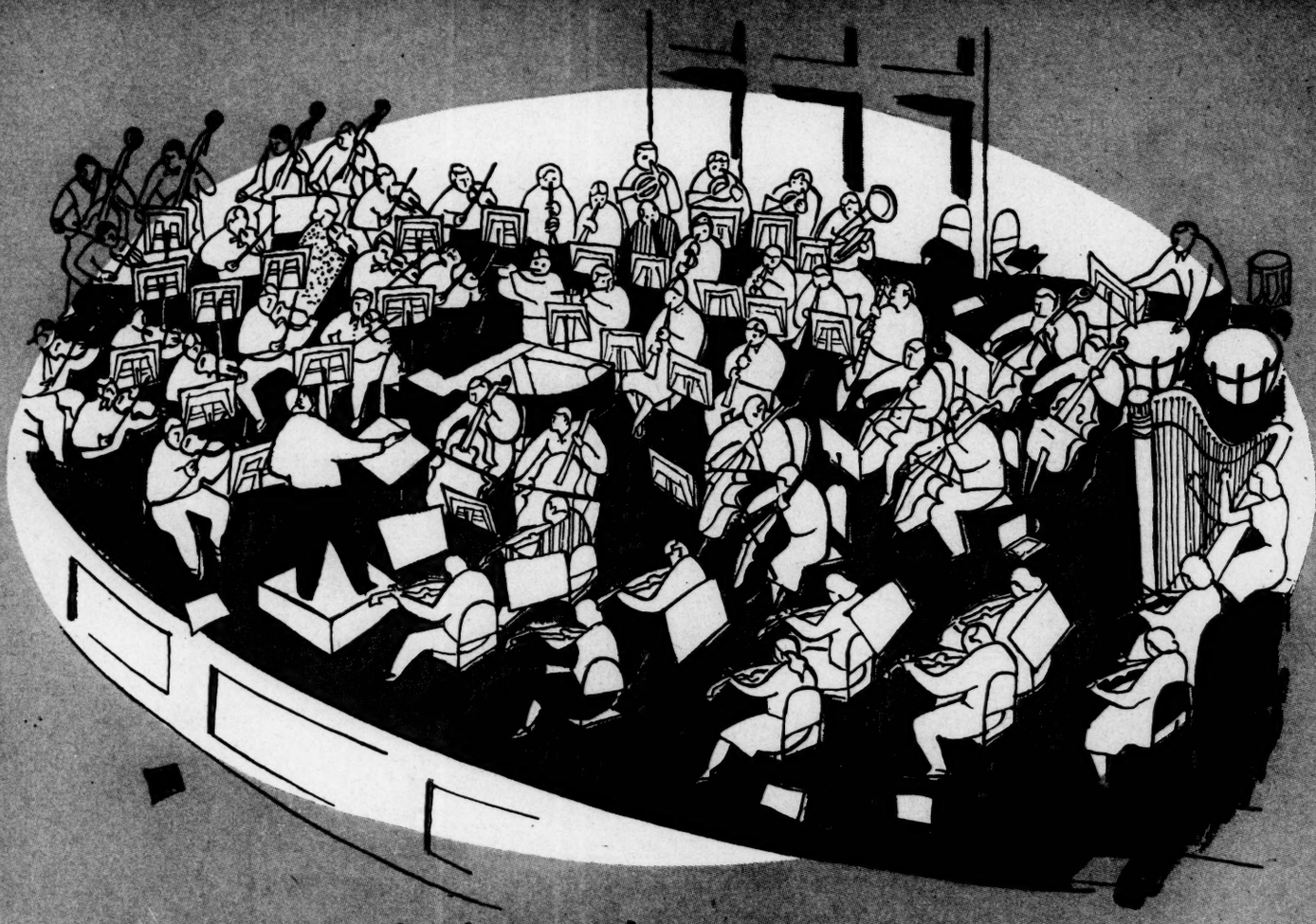
Epinephrine suspended in oil has the disadvantages that because of delayed action it cannot be used when prompt effect is desired as in acute asthmatic attack, and it must be given intramuscularly making self-administration difficult. Aqueous suspensions have a prompt, as well as a prolonged action, and may be self-administered subcutaneously as readily as epinephrine hydrochloride solution.

Naterman, H. L. The Journ. of Allergy. 24:60,1953.

Brewer EST. 1852

For complete reprints of above and sample, send your Rx blank marked 135 P2

BREWER & COMPANY, INC. WORCESTER 8, MASSACHUSETTS U.S.A.



they could stage their own symphony

. . . all the patients who represent the 44 uses for short-acting

NEMBUTAL®

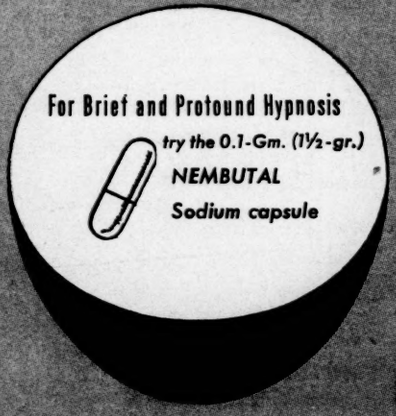
EVER WONDER WHY one drug should survive 23 years of clinical experience (when a lifetime for many is only about five)? Why it should account for 598 published reports? Or more than 44 clinical uses?

Short-acting NEMBUTAL (Pentobarbital, Abbott) is the drug. The reasons why?

1. Short-acting NEMBUTAL can produce any desired degree of cerebral depression—from mild sedation to deep hypnosis.
2. The dosage required is small—only about half that of many other barbiturates.
3. There's less drug to be inactivated, shorter duration of effect, wide margin of safety and little tendency toward morning-after hangover.
4. In equal oral doses, no other barbiturate combines quicker, briefer, more profound effect.

How many of short-acting NEMBUTAL's 44 uses have *you* tried? You'll find details on all in the booklet, "44 Clinical Uses for NEMBUTAL." Write Abbott Laboratories, North Chicago, Ill.

Abbott



1-126

tested

broad-spectrum therapy

Terramycin®

BRAND OF OXYTETRACYCLINE

established

an agent of choice

in the treatment of a wide range of infections due to gram-positive and gram-negative bacteria, spirochetes, rickettsiae, certain large viruses and protozoa.

clinical advantages known

rapid absorption — Within an hour after oral administration in fasting or non-fasting state, effective serum concentrations of Terramycin may be attained.[1] It is widely distributed in body fluids, organs and tissues and diffuses readily through the placental membrane.[2,3]

wide distribution

prompt response — Immediate evidence of Terramycin's efficacy is often obtained by the rapid return of temperature to normal.[4]

excellent toleration — Widely used among patients of all ages, this tested broad-spectrum antibiotic is well tolerated,[5] often when other antibiotics are not.[6]

1. Sayer, R. J., et al.: Am. J. M. Sc. *221*:256 (Mar.) 1951.
2. Welch, H.: Ann. New York Acad. Sc. *53*:253 (Sept.) 1950.
3. Werner, C. A., et al.: Proc. Soc. Exper. Biol. & Med. *74*:261 (June) 1950.
4. Welman, B., et al.: Brit. M. J. *1*:419 (Feb. 23) 1952.
5. Potterfield, T. G., et al.: J. Philadelphia Gen. Hosp. *2*:6 (Jan.) 1951.
6. King, E. Q., et al.: J. A. M. A. *143*:1 (May 6) 1950.

Available in convenient oral, parenteral and topical forms.

Pfizer

PFIZER LABORATORIES, *Brooklyn 6, N. Y.*
Division, Chas. Pfizer & Co., Inc.

EDIOL

An unusually palatable dietary additive, EDIOL can be taken alone and also combined with a variety of foods. Just two tablespoonfuls q.i.d. of this delicious oral fat suspension provide 600 extra calories. For still higher caloric intake, more may be prescribed as required.

EDIOL micronized emulsion of coconut oil (50%) and sucrose (12½%), supplied in bottles of 16 fluid ounces.

caloric boost <u>without</u> gastric burden

Schenley Laboratories, Inc.
New York 1, New York

Upjohn

diarrhea...

Kaopectate

Trademark Reg. U.S. Pat. Off.

Each fluidounce contains:

Kaolin . . . . . 90 grs.

Pectin . . . . . 2 grs.

in an aromatized and carminative vehicle

Available in bottles of 10 oz. and 1 gallon

The Upjohn Company, Kalamazoo, Michigan

Doctor, do you feel that your colleagues are missing important new medical findings by not reading The American Journal of Medicine?

Let us send them a complimentary copy—of course there is no obligation to you or your colleagues. Just fill out the coupon and mail it to us.

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A.J.M.

The American Journal of Medicine

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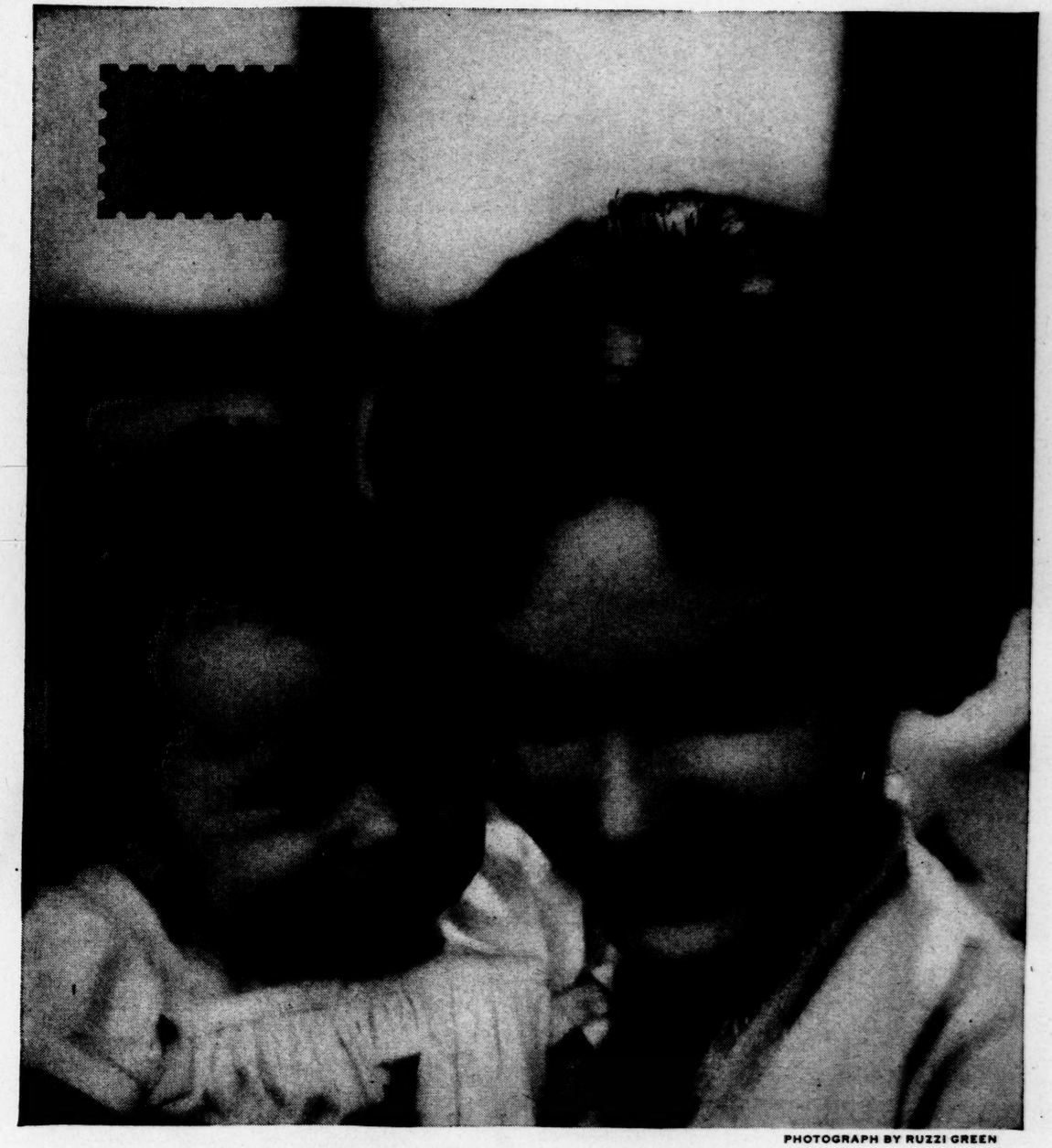

PHOTOGRAPH BY RUZZI GREEN

For little patients... and big ones, too

PENALEV.

SOLUBLE TABLETS POTASSIUM PENICILLIN G

ACTIONS AND USES: Dissolved in a small amount of liquid, PENALEV Tablets make oral penicillin therapy acceptable to small patients who won't swallow tablets. And they also make penicillin dosage easy to regulate in adult patients. PENALEV Tablets are effective in all infections which may be treated with oral penicillin. Also useful for aerosol therapy and prescription compounding.

DOSAGE: According to the type and severity of the infection.

SUPPLIED: In three dosage strengths—50,000, 100,000 and 250,000 unit tablets in vials of 12 and bottles of 100.

PHOTOGRAPH BY PAUL RADKAI

"All children showed prompt clinical improvement."[1]

TABLETS

REMANDEN®

PENICILLIN WITH PROBENECID—THE NEW ORAL "LONGER-ACTING" PENICILLIN

ACTIONS AND USES: REMANDEN is a longer-acting oral penicillin preparation, providing plasma levels which compare favorably with those obtained by the injection of procaine penicillin. Penicillin plasma levels in a group of 20 children treated with REMANDEN were above .03 unit per milliliter three hours after administration — the average was ten times higher than the minimum inhibitory level for the beta-hemolytic streptococcus found in scarlet fever.[1]

TWO DOSAGE STRENGTHS: 100,000 or 250,000 units of crystalline penicillin G and 0.25 Gm. of probenecid (Benemid®) per tablet.

Adults—4 REMANDEN tablets initially, then 2 every 6 or 8 hours.

Children—On the basis of 0.025 Gm. of Benemid probenecid per kg. (2.2 lb.) of body weight—usually 2 to 4 REMANDEN—100 tablets daily.

SUPPLIED: Vials of 12 and bottles of 100.

REFERENCE: 1. J. Pediat. 42:292 (March) 1953.

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among the candidates for COMBANDRIN*

PROTEIN ANABOLIC STEROID HORMONE COMBINATION

...tired elderly patients

With Combandrin, the tired, elderly patient lacking the metabolic support supplied in earlier years by gonadal hormones can often be made stronger, more alert. Formation and retention of protein are promoted, aging bone can be given a "new lease" on life, and mental and emotional reactions may be favorably influenced. More persons can "live"—not merely exist—in their sixties, seventies and eighties. For, the overall results of Combandrin therapy (balanced androgen-estrogen steroid therapy) in the aged "is a lessening of the degenerative state . . ."

Kountz, W. B.: Ann. Int. Med. *35*:1055, 1951.

SUPPLIED: Each cc. contains 1 mg. estradiol benzoate and 20 mg. testosterone propionate in sesame oil, for intramuscular injection. In single-dose disposable Steraject® cartridges and in 10 cc. multiple-dose vials.

Also, Combandrets* — androgen-estrogen combination in convenient tablet form for absorption by transmucosal route.

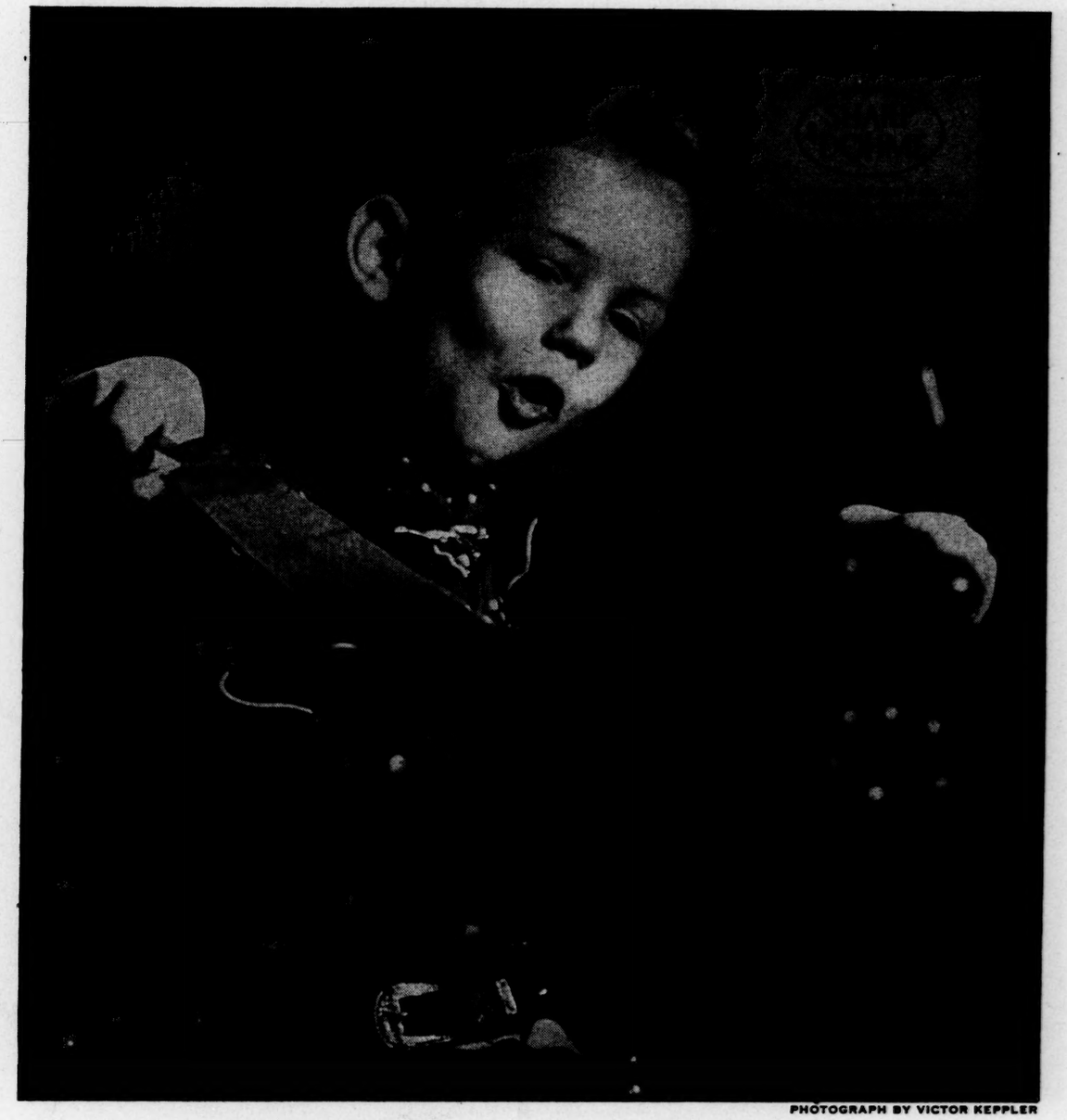
PFIZER SYNTEX PRODUCTS

Pfizer

PFIZER LABORATORIES, *Brooklyn 6, N. Y.*

DIVISION, CHAS. PFIZER & CO., INC.

*TRADEMARK



PHOTOGRAPH BY VICTOR KEPPLER

Puts him back in the saddle again . . .

PENTRESAMIDE®

TRIPLE SULFONAMIDE WITH PENICILLIN

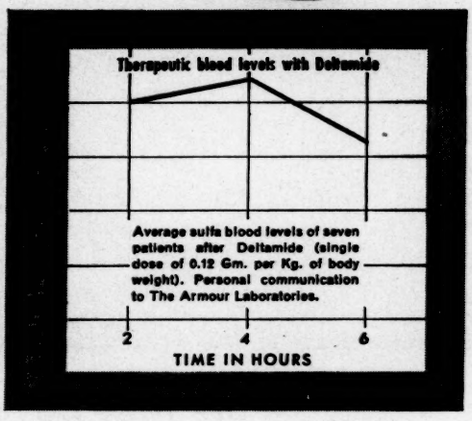
For rapid recovery from susceptible infections, prescribe PENTRESAMIDE—the established antibiotic-sulfonamide therapy.

This easy-to-take oral preparation combines four potent antibacterial agents. It provides synergistic effect...broader antibacterial range ...minimal bacterial resistance...reduced toxicity. In clinical use to combat pneumonia in children, "a single oral dose [produces] prompt improvement...striking therapeutic results."[1]

Quick Information: PENTRESAMIDE-100 and PENTRESAMIDE-250 Tablets provide in each tablet 0.1 Gm. sulfamerazine, 0.2 Gm. each of sulfamethazine and sulfadiazine, with either 100,000 or 250,000 units of potassium penicillin G. Dosage according to body weight, and severity of infection. Schedules on request.

REFERENCE: 1. New York State J Med. 50:2293, 1950.

The synergistic action of Deltamide w/Penicillin promotes faster patient recovery in prevention and control of infections secondary to influenza. In addition, Deltamide w/Penicillin produces effective and well-sustained blood levels.



DELTAMIDE *w/*penicillin

Deltamide w/Penicillin is available in two dosage forms—tablets and pleasant-tasting, chocolate-flavored suspension.

THE NEW QUADRI-SULFA MIXTURES

Each tablet, or each teaspoonful (5 cc.), provides:

Sulfadiazine	0.167 Gm.
Sulfamerazine	0.167 Gm.
Sulfamethazine	0.056 Gm.
Sulfacetamide	0.111 Gm.
Potassium Penicillin G (Buffered)	250,000 units

Tablets: Bottles of 36 and 100.

Powder for Suspension: 60 cc. bottles to provide 2 oz. of suspension by the addition of 40 cc. of water.

DELTAMIDE

the new fourth dimension in sulfa therapy

Each tablet, or each teaspoonful (5 cc.) of pleasant, chocolate-flavored suspension, provides:

Sulfadiazine	0.167 Gm.	Sulfamethazine	0.056 Gm.
Sulfamerazine	0.167 Gm.	Sulfacetamide	0.111 Gm.

Tablets: Bottles of 100 and 1000. **Suspension:** Bottles of 4 oz. and 16 oz.

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for the obese patient . . .

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genuine Obedrin
obtainable
only on
prescription
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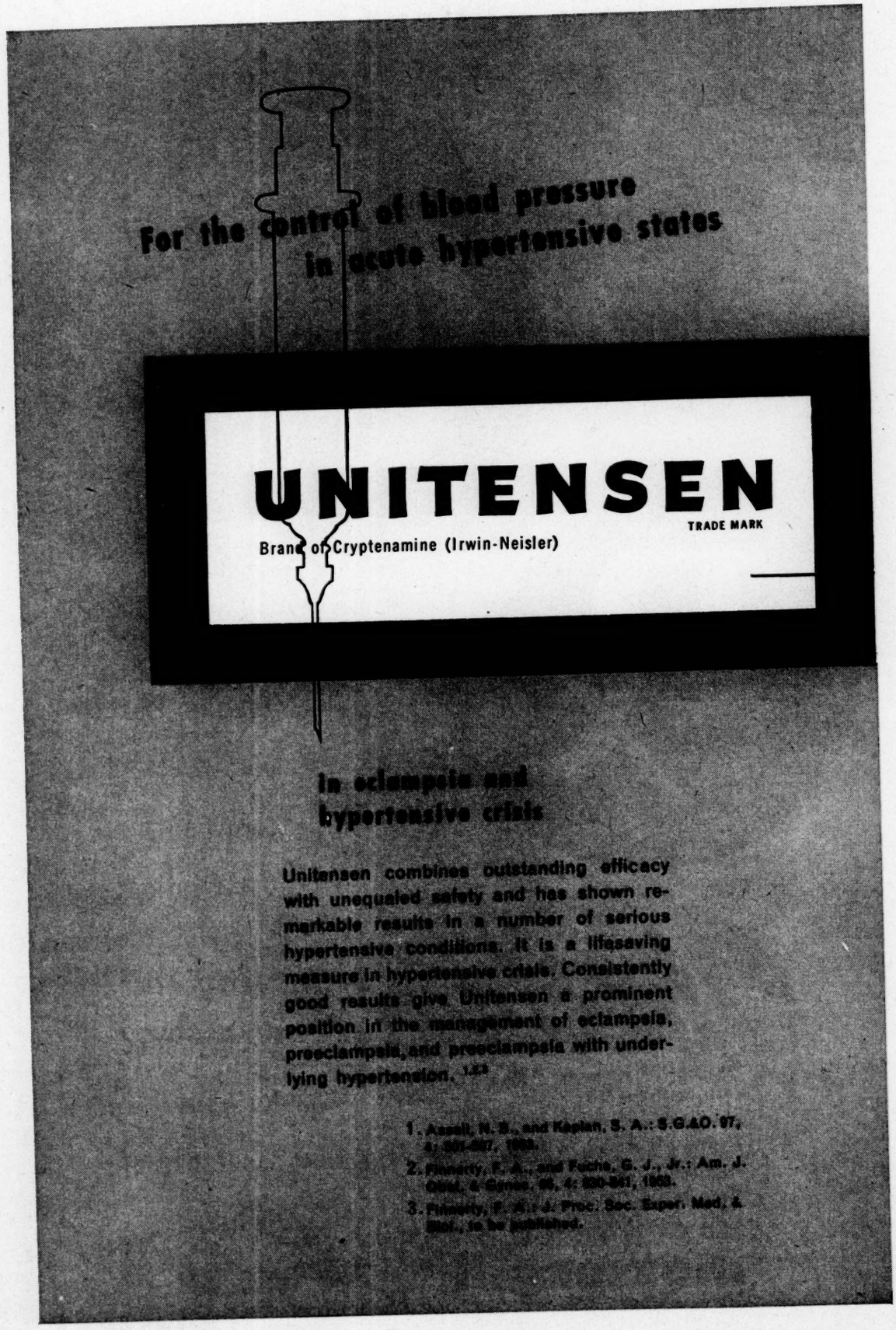
tablets are
monogramed
for your
assurance of
quality

Obedrin

Semoxydrine HCl	5 mg.
(Methamphetamine HCl)	
Pentobarbital	20 mg.
Ascorbic Acid	100 mg.
Thiamine HCl	0.5 mg.
Riboflavin	1 mg.
Niacin	5 mg.

massengill


For the control of blood pressure
in acute hypertensive states
UNITENSEN
TRADE MARK
Brand of Cryptenamine (Irwin-Neisler)
In eclampsia and
hypertensive crisis
Unitensen combines outstanding efficacy with unequaled safety and has shown remarkable results in a number of serious hypertensive conditions. It is a lifesaving measure in hypertensive crisis. Consistently good results give Unitensen a prominent position in the management of eclampsia, preeclampsia, and preeclampsia with underlying hypertension.[1,2,3]
1. Assali, N. S., and Kaplan, S. A.: S.G.&O. 97, 4: 537-557, 1953.
2. Finnerty, F. A., and Fuchs, G. J., Jr.: Am. J. Obst. & Gynec. 66, 4: 830-841, 1953.
3. Finnerty, F. A.: J. Proc. Soc. Exper. Med. & Biol., to be published.

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ADVANTAGES
OF
UNITENSEN

- Of all the known Veratrum alkaloids or Veratrum alkaloid preparations, Unitensen, brand of cryptenamine, is the only one which is double-assayed for a consistent 4:1 ratio between the dose which produces the side effect of vomiting and the dosage level required for hypotensive action.
- Unitensen is easily administered and does not necessitate a complicated dosage schedule.
- Unitensen assures freedom from dangerous side actions. Nausea and vomiting are minimized since dual biologic standardization establishes a uniform ratio of therapeutic to emetic propensity.

THE ONLY
Veratrum
PREPARATION

Assayed for therapeutic effect

Unitensen is assayed in dogs for its effects on blood pressure. The C.S.R.* method is used. In contrast to most bio-assay methods, the C.S.R. assay is not based upon a comparison with a known reference standard, since the C.S.R. end-point serves as an absolute measure of hypotensive potency.

*Carotid Sinus Reflex

Assayed for side effect

The emetic dose of Unitensen is determined in animals. For example, a dose of 0.0075-0.009 mg./kilogram of cryptenamine will lower the blood pressure and block the carotid sinus reflex, whereas 0.02 mg./kilogram is necessary to induce vomiting.

Unitensen (Aqueous) is available at present as a parenteral preparation, containing 2 mg. (200 C.S.R. Units) of Cryptenamine per cc. in 5 cc. multiple dose vials.

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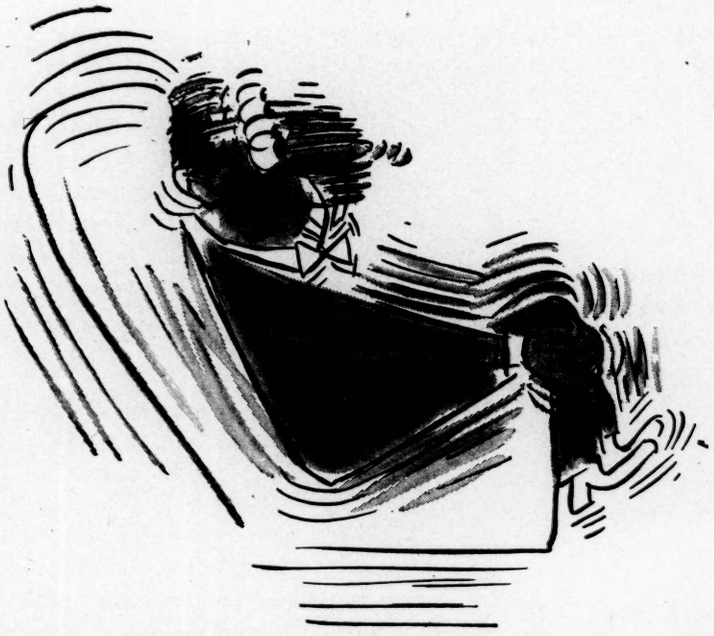

new

for people who travel

Bonamine*

Brand of meclizine hydrochloride

the first compound effective against motion sickness in a single daily dose

most prolonged action

Bonamine is the only motion-sickness preventive which is effective in a *single daily dose.* Just two 25 mg. tablets (50 mg.) will provide adequate protection against all types of motion sickness—car or boat, train or plane—for a *full 24 hours in most persons.*

few side effects

Clinical studies have shown, in case after case, that relatively few of the patients experienced the usual side effects observed with other motion-sickness remedies: less drowsiness, dullness, headache, dryness of the mouth, etc. In addition, Bonamine is tasteless and acceptable to patients of all ages.

Supplied: 25 mg. tablets.

*TRADEMARK

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Triple antibiotic for infections in the TROCHE ZONE

pharyngitis
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and especially in non-febrile sore throat

WYBIOTIC Troches are bactericidal against both gram-negative and gram-positive organisms commonly found in the mouth and throat. WYBIOTIC Troches contain no penicillin.

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Note the potency!

Zinc Bacitracin . . . . . 300 units
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Supplied: Cans of 48 troches

*Trademark of related company

PHOTOGRAPH BY CHARLES KERLEE

Pernicious anemia patient "happy to work again"*

REDISOL®

CRYSTALLINE VITAMIN B_{12}

His job required precision. Vitamin B_{12} remitted the disabling symptoms of pernicious anemia... put him back at work.*

In many cases of anemia, REDISOL—pure vitamin B_{12}, produces similar remarkable results. Hemopoiesis is stimulated, associated neuritic conditions improve.

Small doses of vitamin B_{12} produce the same response in pernicious anemia as injections of potent liver extracts.

Clinical evidence also shows the value of vitamin B_{12} in tropical and non-tropical sprue. In trigeminal neuralgia, pain is remarkably relieved.

Quick Information: REDISOL supplies vitamin B_{12} in a complete range of dosage forms for every practical use. REDISOL *Tablets*, 25 and 50 mcg. in bottles of 36 and 100. REDISOL *Injectable*, 30 and 100 mcg. per cc. in 10 cc. vials—also 1,000 mcg. per cc. in 1 cc. vials. *Elixir*, 5 mcg. per 5 cc. in pint SPASAVER® and gallon bottles.

*From a case report J.A.M.A. 153:191, 1953.

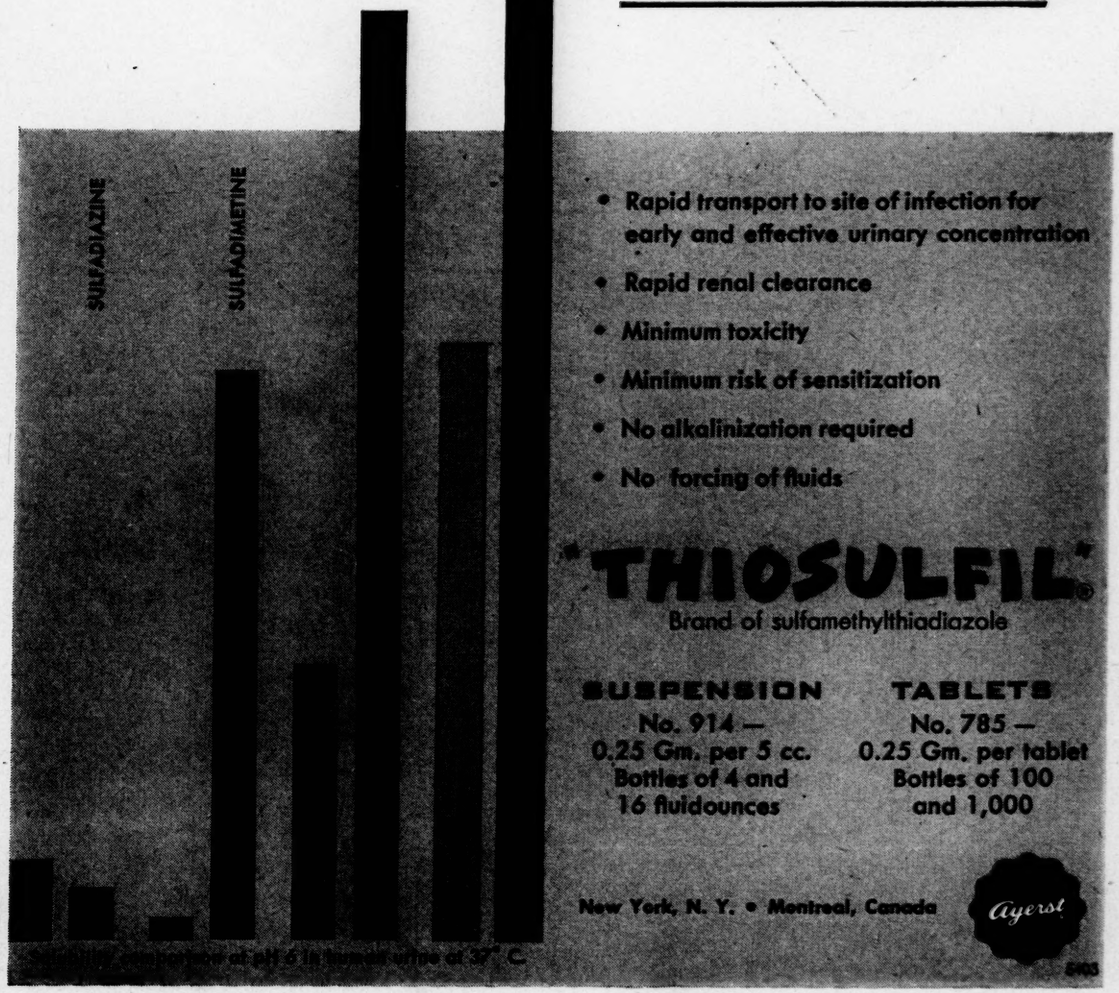
SUITABILITY *depends upon* SOLUBILITY

Laboratory studies have demonstrated the greater solubility of "Thiosulfil" as compared with the other three leading sulfonamides prescribed in urinary tract infections.
This obvious advantage, added to high bacteriostatic activity and a low acetylation rate makes

"THIOSULFIL"

the safest and m effective sulfonamide yet presented for

urinary tract infections



- **Rapid transport to site of infection for early and effective urinary concentration**
- **Rapid renal clearance**
- **Minimum toxicity**
- **Minimum risk of sensitization**
- **No alkalinization required**
- **No forcing of fluids**

"THIOSULFIL"®

Brand of sulfamethylthiadiazole

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No. 914 —
0.25 Gm. per 5 cc.
Bottles of 4 and
16 fluidounces

TABLETS
No. 785 —
0.25 Gm. per tablet
Bottles of 100
and 1,000

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Nephenalin®
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First, under tongue for quick asthma relief

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Then, swallow tablet for prolonged asthma control

from theophylline, ephedrine, phenobarbital, contained in tablet core

NEPHENALIN, the "relay-action" tablet combining two widely prescribed, complementary anti-asthmatics, is now available in two potencies: the familiar square, *purple* tablet for adults, and the smaller square, *red* tablet for children. Since a single NEPHENALIN tablet provides quick asthma relief, thereby often replacing the nebulizer, and since relief lasts about four hours, many asthmatic patients will find it the most convenient and efficient anti-asthmatic they have ever used. Bottles of 20 and 100 tablets.

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